REMARKS

The Amendments

Claim 3 has been amended to incorporate the limitations of claim 4. Claim 4 has been cancelled as redundant. Claim 9 has been amended for better antecedent basis. Non-elected claims 14-36 have been cancelled without prejudice.

The Information Disclosure Statement

The Office Action states:

> The information disclosure statement filed August 24, 2004 (24 sheets) fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. Please refer to those citations that were not considered as indicated on the 1449 with a strikethrough. The information disclosure statements filed on June 10, 2005 (1 sheet); June 27, 2005 (2 sheets); September 20, 2005 (1 sheet); and December 12, 2005 (2 sheets) have been reviewed and considered, see enclosed copies of PTO FORMS 1449.

Substitute copies of the publications that were lined through in compliance with Rule 37 CFR 1.98(a) (2) are being provided along with a substitute Patent Office Form SB-08a listing these references. Consideration of these references is respectfully requested.

The Rejection Under Section 112, first paragraph

Claim 3 has been rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office Action states:

> The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *Regents of the University of California v. Eli Lilly & Co.,* 119 F. 3d 1559, 1568 (Fed. Cir. 1997), *cert. denied,* 523 U.S. 1089, 118 S.Ct. 1548 (1980), holds that an adequate written description requires a

> precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, "Written Description" Requirement ("Guidelines'"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, "including, inter alia, "functional characteristics when coupled with a known or disclosed correlation between function and structure.. . ." *Enzo Biochem, Inc. v. Gen-Probe.*, 296 F.3d, 316, 1324-25 (Fed. Cir. 2002) (quoting Guidelines, 66 Fed. Reg. At 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G. D. Searle & Co.,* 249 F. Supp.2d 216, 225 (W. D. N. Y 2003).
>
> There is insufficient descriptive support for the ensuing phrase, "peripheral metabolism inhibitor." In addition, the instant specification does not describe what is meant by the phrase, "peripheral metabolism inhibitor." Structural identifying characteristics of the phrase, "peripheral metabolism inhibitor." There is no evidence that there is any per se structure/function relationship between the phrase, "peripheral metabolism inhibitor." The instant specification does not provide an adequate written description for the phrase, "peripheral metabolism inhibitor." In addition these terms are described illustratively in the instant specification. In fact, there is only an adequate written description for the combined administration of the "peripheral metabolism inhibitor" as adequately described in claim 4. Accordingly, these claims fail to comply with the written description requirement.

Claim 3 has been amended to incorporate the limitations of claim 4. Claim 4 has been cancelled as redundant. The Office Action states that claim 4 provides an adequate written description, and thus it is submitted that the rejection has been overcome by this amendment.

The Rejection Under Section 112, Second Paragraph

Claim 9 has been rejected under Section 112, Second Paragraph. The Office Action States: "Claim 9 recites the limitation 'said movement disorder' in line 1 of claim 9. There is insufficient antecedent basis for this limitation in the claim because claim 1 does not specifically utilize the language of the limitation "said movement disorder."

Claim 9 has been amended to change "said movement disorder" to "said condition" for which antecedent support is provided in claim 1, and it is submitted that this amendment overcomes the rejection and withdrawal thereof is respectfully requested.

The Rejection Under Section 103(a) Over Roberts-Lewis et al. and Di Rocco et al.

Claims 1-13 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Roberts-Lewis et al. of U.S. Patent No. 5,430,039 in view of Di Rocco et al. of U.S. Patent No. 5,496,836. The Office Action states:

> Roberts-Lewis et al. teach it is known in the neurological art of pharmacology that chloroquine or hydroxychloroquine are used in the treatment of neurological disorders, namely Parkinson's Disease, (see column 2, lines 22-34 and column 8, lines 40-60). Di Rocco et al. teach of treating movement disorders, such as Parkinson's Disease, with the administration of cimetidine, (see column 5, lines 20-45 and from column *6,* line 23 to column 7, line 11). "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven,* 626 F.2d 846,850,205 USPQ 1069, 1072 (CCPA 1980). Moreover, it is well within the level of the skilled artisan to determine optimal modes and methods of administration as well as the procedures for making pharmaceutical compositions having the optimum therapeutic dosage while minimizing adverse and/or unwanted side effects.

This rejection is respectfully traversed. It is noted that this reference was cited and successfully overcome in the grandparent application hereof (Patent No. 6,417,177).

The '039 Patent does not enable the treatment of Parkinson's or other neurological condition with chloroquine compounds.

The Roberts-Lewis patent (No. 5,430,039) was cited during examination of the grandparent application hereof for allegedly treating a method of inhibiting neuronal cell death resulting from a disorder of the central or peripheral nervous system by administering chloroquine. Applicant showed that the reference was not properly applied to the claims that issued in the grandparent case as Patent No. 6,417,177. Applicant submits (1) that the '039 patent does not enablingly show the use of chloroquine for treating brain disorders (and therefore is not properly cited as the basis of an obviousness rejection); (2) that the Di Rocco et al. patent (No. 5,496,836) also does not enable the treatment of Parkinson's using cimetidine (and therefore is not properly cited as the basis of an obviousness rejection); and (3) that there is no motivation in the references, nor in the art as a whole for combining these references to formulate an obviousness rejection. In fact, the art as a whole teaches against the specific combination of chloroquine and cimetidine (at the doses specified in the Di Rocco et al. patent) to treat movement disorders, and also teaches against the use of targeting agents to target chloroquine compounds to the brain.

First it will be shown that the primary reference (the '039 patent) is not enabled and therefore is not available as a reference; that the Patent and Trademark Office has determined this; that the '039 Patent teaches a mechanism of action that would worsen Parkinson's symptoms; and that the '039 patent does not enable the use of chloroquine compounds to treat any neurological condition, even cerebral ischemia, the condition to which this cited patent is primarily directed.

The Patent Office's determination that the '039 patent did not enable treating any brain disorder other than cerebral ischemia is of record in the file history of that patent, portions of which are submitted herein as Exhibits A and B. The '039 patent originally attempted to claim a method for inhibiting neuronal cell death in a mammal resulting from a disorder of the central or peripheral nervous system comprising administering to said mammal mepacrine, chloroquine or hydroxychloroquine (free of colchicine). Treatment of Parkinson's Disease, Huntington's disease, AIDS dementia, epilepsy, motor neuron diseases, peripheral nerve degeneration and head and spinal cord injuries was specified in original, as-filed dependent claim 5 of the '39 patent. This claim was rejected in the first Office Action as inoperative and non-enabled (see Exhibit A). The first Office Action issued in the '039 patent (Exhibit B) rejected claim 5, stating at page 3: "The claims set forth numerous conditions treatable with the instant compositions, but fail to show such treatments as effective against the maladies set forth in the instant claims," and: "[T]he disclosure is enabling only for claims limited to various necrotic conditions." In the claims as allowed and issued, reference to treating Parkinson's Disease and the other conditions mentioned in as-filed claim 5 had been canceled, and there was no mention of "inhibiting neuronal cell death"; rather the claims were strictly limited to treatment of "necrosis resulting from a cerebral ischemia." (Allowed dependent claims 6 and 7 referred to necrosis occurring in the *substantia nigra* (claim 6) and at a dopaminergic neuron (claim 7) resulting from cerebral ischemia.)

The prosecution history of the '039 patent thus shows that the Patent and Trademark Office determined that the disclosure was not enabling for treatment of Parkinson's Disease or brain disorders other than necrosis caused by cerebral ischemia. Parkinson's Disease is caused by apoptotic cell death rather than the

necrotic cell death taught in the '039 patent (See the present Specification, first full paragraph on page 4). This provides further evidence that the '039 patent does not enable the use of chloroquine to treat Parkinson's.

Further, the '039 patent fails to enable the use of chloroquine to treat Parkinson's Disease because it teaches a mechanism of action that would worsen Parkinson's symptoms. The way results were evaluated in the '039 patent involved measuring spectrin breakdown following damage to the brain caused by kainate infusion into the brain or tying off blood vessels in rodent models. The use of spectrin breakdown measurement to evaluate results of administration of the therapeutic compounds was based on the patentee's theory that ischemia results in spectrin breakdown (col. 7, lines 41-43), and that this spectrin breakdown is caused by excitatory amino acids (EAA) which lead to calcium-related neuronal death (col. 1, lines 40-60 and col. 3, lines 55-65). The treatment taught in the patent was designed to prevent calcium from entering the cells (col. 2, lines 35-42, paragraph bridging columns 8 and 9) and thereby prevent necrosis.

However, it is known to the art that the use of calcium channel blockers as taught in the '039 patent exacerbates Parkinson's Disease. (See Abstracts of Takahashi, A. and Murakami, M. (1993), "Drug-induced movement disorders," Nippon rinsho 51(11):2929-2934; Garcia Ruiz PJ, et al. (1992), "Cinnarizine-induced parkinsonism in primates," Clinical neuropharmacology 15(1):19-26; Negrotti A., et al. (1992), "Calcium-entry blockers-induced parkinsonism: possible role of inherited susceptibility," Neurotoxicology 13(1):261-264; Kuzuhara S.L., et al. (1989), "Parkinsonism, depression and akathisia induced by flunarizine, a calcium entry blockade—report of 31 cases," Rinsho shinkeigaku 29(6):681-686, submitted herewith as Exhibit C.) This is another reason why one skilled in the art would consider that the disclosure of the '039 patent does not enable the use of chloroquine for treating Parkinson's Disease.

The '039 patent does not even enable the use of chloroquine for treating cerebral ischemia, the condition it is primarily concerned with (see its claims). The Declaration by Dr. Patricia L. Stranahan, M.D., Ph.D., an experienced pathologist and professor of pathology, submitted in the parent application (now Patent No. 6,417,177, provides her expert opinion that the '039 patent does not enable the use of chloroquine to treat necrosis due to cerebral ischemia. This Declaration is submitted herein as Exhibit D.; however, rather than including her voluminous CV as an attachment to said Declaration, a brief biographical summary of her education and experience is provided, taken from her University website.

The examples in the '039 patent show treatment of brain tissue with mepacrine *prior to or at the time of* damaging the tissue with kainate or tying off blood vessels to simulate cerebral ischemia (the patent asserts that chloroquine can be substituted for mepacrine).

Neural damage, *e.g.* resulting from a five-minute occlusion, would not be expected to show up until about 7-28 days after cutting off blood flow. However, in the '039 patent, results were evaluated only 24 hours after the event in rats and 4 to 6 days after the event in gerbils, while the art teaches that neural protective effects seen earlier than 7-28 days after the occlusion tend to evaporate--indicating a mere postponement of injury rather than real protection.

Further, rats and gerbils, the animals in which results in the '039 patent were generated, are not good animal models for cerebral ischemia in humans. Gerbils are notorious for false positive results in studies involving neural protection, and both rats and gerbils are poor models for cerebral ischemia because reperfusion injury (which occurs in humans by 24 hours, at about 50%) does not occur in rodents.

It is well recognized in the art that as a practical matter in cerebral ischemia, treatment is not undertaken until at least about 6 to about 24 hours after the event.

Pretreating patients for cerebral ischemia, as was done in the examples of the '039 patent, is not possible because these events are unpredictable.

Treating patients for cerebral ischemia within less than about ten to fifteen minutes after the event is also not possible because typically patients have not reached a treatment facility within such a short period of time.

Further, those of skill in the art are aware that chloroquine causes hypotension and psychiatric effects such as hallucinations. This is another reason why medical personnel who are treating patients for cerebral ischemia would not consider it reasonable to administer chloroquine, and in any event would not administer it before a diagnosis had been made.

Moreover, the art as a whole teaches that administration of chloroquine for treatment of cerebral ischemia after the first ten minutes will damage the neurons through nitric oxide generation rather than having a protective effect.

As is known to the art (see Stranahan Declaration), cerebral ischemia immediately begins a cascade in which cytokines tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) are induced. These degrade Inhibitor κB-α (I-κB-α) which inhibits production of nuclear factor κB (NF-κB). NF-κB stimulates an inflammatory cascade producing O_2^- and other reactive oxygen species such as NO and $ONOO^-$ which cause extensive neural damage. Eventually, after NF-κB

reaches the cell nucleus, it acts to cause production of I-κB-α messenger RNA to produce the inhibitor I-κB-α and damp down the inflammatory response and production of reactive species, however, not before a great deal of neural damage has been done.

Chloroquine is a potent inhibitor of TNF-α and IL-6. If administered prior to the beginning of the cytokine cascade initiated by a cerebral ischemic event, chloroquine prevents degradation of I-κB-α which inhibits NF-κB and prevents formation of the reactive species which are so damaging to neurons.

However, if chloroquine is administered after the ischemic event, when cytokine production has been initiated (which happens immediately) it prevents synthesis of I-κB-α, thus allowing enhanced, unchecked production of NF-κB and enhanced production of damaging reactive species. Research shows that I-κB-α is completely gone within 15 minutes after chloroquine administration.

Thus, given before an ischemic event, chloroquine can prevent neural damage; given after an ischemic event, it *enhances* neural damage.

So the only way chloroquine could function as an effective treatment for cerebral ischemia would be to administer it *before* the event, or within about ten to fifteen minutes after the event, *i.e.* before production of cytokines leading to production of reactive oxygen and nitric oxide species begins. If it is administered before the event, it will prevent production of these harmful species and consequent neural damage. Administration of chloroquine after the event will enhance neural damage by preventing synthesis of I-κB-α.

From this it can be seen that when chloroquine is administered before the event, as in the '039 patent, it will prevent neural damage by preventing degradation of I-κB-α, and administration of further chloroquine after the event will not have any further effect because although it prevents synthesis of more I-κB-α, more I-κB-α is not needed because the I-κB-α already present has not been degraded.

Therefore, the '039 patent, which is based on experimental evidence showing treatment before or simultaneously with neuronal damage, does not enable the treatment of cerebral ischemia using chloroquine because in practice chloroquine cannot be administered before the event or within less than about six hours after the event. If it is administered later than that it will further damage the cells.

The teachings of this patent therefore do not enable one skilled in the art, who is aware of the foregoing harmful effects of chloroquine, to treat cerebral ischemia using chloroquine.

Thus, the '039 patent, as a non-enabled reference, is not properly cited as a reference against the present disclosure.

The '836 Patent does not enable, and in fact teaches against treatment of Parkinson's Disease using cimetidine.

It will be shown that the '836 patent does not enable, and in fact would teach one skilled in the art that cimetidine in the dosages described in that patent is not effective against movement disorders, and that in fact it is a cause of movement disorders.

The '836 Patent contains contradictory teachings regarding cimetidine, including teaching that cimetidine *reduces* locomotor activity.

In the paragraph bridging columns 3 and 4, citing an earlier publication, the patent teaches that cimetidine had been shown to *reduce* locomotor activity. Reduction of locomotor activity is not desirable in the treatment of Parkinson's patients, whose motor functions tend to "freeze." (See also, Takahashi, A. et al. (1993), "Drug-induced Movement Disorders," Nippon rinsho (JAPAN) 51(11):2929-34 – Exhibit C, first Abstract.) Levodopa and other dopamine agonists used to treat Parkinson's *increase* locomotor activity. Although the patent names cimetidine (in only one place) as a compound related to famotidine that would be useful to treat movement disorders, it provides no data to overcome the art-known reduction of locomotor activity caused by cimetidine. Thus, one skilled in the art would conclude that the preponderance of scientific evidence disclosed in this patent indicates that cimetidine would not be useful to treat Parkinson's Disease.

Note that the '836 patent also discloses at col. 4, lines 55-56 that: "No motor effects of these compounds had been documented prior to the present invention." This is in direct contradiction to the citation in the patent of prior art showing that cimetidine had been shown to reduce locomotor activity. This would indicate a lack of focus on cimetidine (as opposed to famotidine, the only compound actually tested), and one skilled in the art would reasonably conclude that the "related compounds" had only been included in the patent disclosure for the sake of broadening the patent, and that nothing was actually known about their efficacy.

Further, the '836 patent teaches that famotidine and related compounds such as cimetidine are administered in conjunction with the subject's previous treatment regimen (paragraph bridging cols. 8 and 9). Thus it would not be clear to one skilled in the art that the reported improvement in symptoms was due to the famotidine.

The '836 patent fails to claim treatment of Parkinson's.

The next-to-last clause of claim 1 specifically excludes Parkinson's Disease from the list of conditions treated by famotidine or a famotidine-related compound.

The patent '836 patent discloses dosages that, applied to cimetidine, would be toxic and cause movement disorders.

Exhibit E, a printout from the MicroMedEx database, Section 4, states that famotidine is 40-60 times more potent than cimetidine. See also Exhibit F, a printout from the MicroMedEx database, Section 4.4. Also see Exhibit G, a comparative chart printed out from the MicroMedEx database comparing dosages of famotidine and cimetidine. The '836 patent teaches dosage of compounds related to famotidine as follows:

> An equivalent amount of a famotidine-related compound refers to an amount of the famotidine-related compound having essentially the same functional activity as the specified amount of famotidine. The determination of what constitutes an "equivalent amount" of a famotidine-related compound may take into consideration how the potency and bioavailability of the famotidine-related compound compares to the potency and bioavailability of famotidine. For example, if a famotidine-related compound has twice the potency and the same bioavailability characteristics as famotidine, then if an initial dose of between 20-160 mg famotidine is recommended, the recommended initial dose of the famotidine-related compound would be 10-80 mg per day. [Col. 8, lines 18-32.]

Since famotidine is 40 to 60 times as potent as cimetidine, it would have to be administered in dosages of 800 to 9600 mg per day to provide bioavailability equivalent to famotidine bioavailability. This is outside the range of effective dosages for cimetidine disclosed and claimed herein, *i.e.*, 400 - 600 mg per day (Specification, page 15, third full paragraph).

Administering cimetidine in dosages of 800 mg per day and higher would be likely to cause toxic effects, especially in Parkinson's patients who are generally elderly. Exhibit H, "M. Sonnenblick, et al. "Neurological and psychiatric side effects of cimetidine—report of 3 cases with review of the literature" discloses that at doses of 800 to 1200 mg per day, cimetidine caused confusion, psychomotor restlessness, hallucinations, disorientation, stupor, coma, convulsions, neurological deficits and neuropathies. Exhibit I, M.E. Edmonds, et al. (1979), "Cimetidine: does neurotoxicity occur?," Report of three cases," Journal of the Royal Society of Medicine 72:172-175, discloses that adverse neurotoxic effects occurred with cimetidine dosages of 600 to 800 mg per day.

One skilled in the art would therefore hesitate to use cimetidine at the dosages required by the '836 patent to treat Parkinson's patients. By teaching the use of such high doses of cimetidine, the '836 patent teaches away from the use of cimetidine for treatment of Parkinson's Disease.

One skilled in the art would discredit the teachings of the '836 patent with respect to cimetidine.

As discussed above, the '836 patent contains self-contradictory statements about cimetidine's effectiveness, which would cause one skilled in the art to discredit its teaching that cimetidine would be useful to treat movement disorders. In addition, in the paragraph bridging columns 7 and 8, the '836 patent teaches that famotidine-related compounds may

be administered in conjunction with other agents including trihexyphenidyl hydrochloride, benztropine mesylate, biperiden lactate and diphenhydramine hydrochloride. In several publications that show that cimetidine causes movement disorders (Exhibit J, Romisher, S. et al. (1987), "Tagamet®-Induced Acute Dystonia," Annals of Emergency Medicine 1162:115-117, and Exhibit K, Peiris, R. and Peckler, B.F. (2001), "Cimetidine-Induced Dystonic Reaction," The Journal of Emergency Medicine 21(1):27-29), these compounds are reported as being administered as *antidotes* to movement disorders *caused by cimetidine*. To administer a compound known to cause a movement disorder in order to treat a movement disorder would be considered ridiculous to one skilled in the art. This folly is compounded by the teaching in the '836 patent that cimetidine should be co-administered with its known antidotes. Thus one skilled in the art would discredit the teachings of the '836 patent with respect to cimetidine.

The art as a whole teaches against administering chloroquine with cimetidine for the purposes recited in the '836 patent.

The '836 patent defines its effective compounds as H_2 antagonists (col. 5, lines 42-43). The patent also discloses in section 2.4, bridging columns 3 and 4, that other histamine antagonists have been used to treat Parkinson's Disease. However, chloroquine has the opposite effect, in that it potentiates histamine. Exhibit L, abstract of Pacifici, G.M. et al. (1992), "Histamine N-methyl transferase: inhibition by drugs," British Journal of Clinical Pharmacology 34(4):322-327, is one of a number of articles that shows that choroquine inhibits histamine N-methyl transferase. As is known in the art, histamine N-methyltransferase inactivates histamine. See Exhibit M, abstract of K. Yamauchi, et al. (1994), "Structure and function of human histamine N-methyltransferase: critical enzyme in histamine metabolism in airway," Am. J. Physiol. Lung Cell Mol. Physiol

267:L342-L349. Thus, inhibition of N-methyl transferase by chloroquine would upregulate histamine, thereby producing an effect exactly *opposite* to the effect desired by the '836 patent, of antagonizing histamine. Thus, one skilled in the art, knowing the effects of both cimetidine and chloroquine on histamine metabolism, would not wish to combine a reference teaching the use of cimetidine as a histamine antagonist for treating Parkinson's with a reference teaching administering chloroquine.

Thus, not only is there a lack of motivation in references for combining them, there is positive teaching in the art that the references should not be combined. No *prima facie* case of obviousness has therefore been made out.

The art lacks motivation for mixing, linking or complexing chloroquine compounds with any targeting agent.

The art does not teach the use of chloroquine compounds with targeting agents for any purpose. None of the cited art teaches, suggests, or suggests a need for using a targeting agent to provide enhanced amounts of chloroquine to the brain. In fact, as discussed below, the art as a whole teaches against the use of such targeting agents. As discussed above, the '039 patent teaches a mechanism of action (inhibiting necrosis by reducing calcium uptake by cells) which would worsen Parkinson's symptoms, the Patent and Trademark Office has determined on the record that the disclosure of the '039 patent does not enable treatment of Parkinson's. The Di Rocco patent contains no suggestion of using chloroquine with famotidine or famotidine-related compounds such as cimetidine to improve symptoms of Parkinson's Disease.

Even if the '039 patent enablingly taught the use of chloroquine to treat cerebral ischemia in the *substantia nigra* and at dopamine neurons (which it does not), this would not provide motivation for adding a targeting agent to chloroquine to target it to these areas, for the following reasons:

The *substantia nigra* is already known to be a target for chloroquine. Thus one skilled in the art would not consider it necessary to provide additional chloroquine to the brain through the use of a targeting agent. As shown in Donatelli, P. et al. (1994), "Stereoselective inhibition by chloroquine of histamine *N*-methyltransferase in the human liver and brain," *Eur. J. Clin. Pharmacol.* 47:345-349 (of record), chloroquine is targeted to the brain without the use of targeting agents. Further, Lowrey, A.H. et al. (1997), "Modeling Drug-Melanin Interaction with Theoretical Linear solvation Energy Relationships," *Pigment Cell Res.* 10:251-256 (of record) teaches (p. 251, col. 1) that neuromelanin is found in the *substantia nigra*, and (p. 255, cols. 1-2), percent uptake of chloroquine by melanin is 85.5%.

Since the brain, and in particular the *substantia nigra*, is already a very efficient target for chloroquine, one skilled in the art would not be motivated to add a targeting agent to chloroquine to target it to the brain.

The '039 patent contains no suggestion that the dosages of chloroquine it teaches are insufficient. Thus one skilled in the art would not consider an additional targeting agent necessary. The '039 patent does not indicate that providing appropriate dosages of chloroquine requires any special consideration. In fact, it refers to "skill in the art" for determining appropriate dosage amounts (col. 8, lines 56-60). Since the '039 patent teaches administration of chloroquine

without targeting agents, teaches that such administration is sufficient, and fails to suggest any necessity that the amount of chloroquine reaching the brain should somehow be enhanced, it fails to motivate one skilled in the art to combine chloroquine with a targeting agent.

Publications teaching use of chloroquine to treat brain disorders do not suggest the necessity for using targeting agents. Neither the '039 patent nor other patents or publications which describe the use of chloroquine compounds to treat brain conditions suggest the necessity for use of a targeting agent to target chloroquine to the brain. Such publications include the following, all of record herein: U.S. Patent 5,624,938 (of record); Shields, D.C., et al. (1999), "A putative mechanism of demyelination in multiple sclerosis by proteolytic enzyme, calpain," *Proc. Natl. Acad. Sci. USA* 96:11486-11491, which teaches use of chloroquine to treat multiple sclerosis; Rosner, I. And Legros, J. (1967), "Hydroxychloroquine and cortical resistance to anoxia due to asphyxia," *Therapie* XXII:355-360, which suggests use of hydroxychloroquine to correct post-anoxic motor disturbances of ischemic origin, but does not teach or suggest the need for a targeting agent; Sharma, O. (1998), "Effectiveness of Choroquine and Hydroxychloroquine in Treating Selected Patients With Sarcoidosis with Neurological Involvement," *Archives of Neurology* 55(9):1248-1254, which suggests the use of choroquine compounds to treat sarcoidosis, but does not suggest that a targeting agent is necessary; Hagihara, N., et al. (2000), "Vascular protection by Choroquine during Brain Tumor Therapy with Tf-CRM107," *Cancer Research* 60:230-234, which suggests the *systemic* administration of chloroquine for intracerebral chemotherapy, but does not suggest that a targeting agent is necessary; Aisen, P.S. (1997), "Inflammation and Alzheimer's disease: mechanisms and therapeutic strategies," *Gerontology* 43(1-2):143-149 and related grant abstracts, which suggest the use of chloroquine for treating Alzheimer's, but do not suggest any need for targeting agents.

It is submitted that the work of these numerous reputable scientists, whose peer-reviewed publications do not suggest the need for targeting agents when treating brain conditions with chloroquine, would teach one skilled in the art that targeting agents for chloroquine are not required when chloroquine is to be used to treat areas of the brain. Thus, the skilled worker would not be motivated to combine chloroquine compounds with targeting agents.

Chloroquine is known to the art to have severe psychiatric side-effects. Numerous publications provide evidence that chloroquine has severe psychiatric side effects. See, *e.g.*, the following publications, which are of record herein: Good, M.I. and Shader, R.I. (1982), "Lethality and behavioral side effects of chloroquine," *Journal of Clinical Psychopharmacology* 2(1):40-47; Good, M.I. and Shader, R.I. (1977), "Behavioral toxicity and equivocal suicide associated with chloroquine and its derivatives," *American Journal of Psychiatry* 134(7):798-60; Bhatia, M.S. (1991), "Chloroquine-induced psychiatric complications," *British Journal of Psychiatry* 159(Nov):735 (Abstract); Lovestone, S. (1991), "Chloroquine-induced mania," *British Journal of Psychiatry* 159(Jul):164-165 (Abstract); Garg, P., et al. (1990), "Toxic psychosis due to chloroquine: Not uncommon in children," *Clinical Pediatrics* 29(8):448-450; Bhatia, M.S. et al. (1988), "Capgras syndrome in chloroquine induced psychosis," *Indian Journal of Psychiatry* 30(3):311-313 (Abstract); and Tedeschi, M. (1983), "A case of acute psychosis due to Chloroquine," *Information Psychiatrique* 59(9):1191-1197 (Abstract).

In view of all these publications showing how dangerous it is to administer chloroquine to the brain, one skilled in the art would believe potentiating the action of chloroquine in the brain was contraindicated. [It should be noted that because Parkinson's patients have lost over 80% of their dopaminergic neurons, use of a potentiating agent in the present invention does not generally lead to such psychiatric side effects.]

It is known to the art that plasma levels of chloroquine are correlated to effectiveness of chloroquine in protecting against administration of toxic MPP+ to the brain. D'Amato, R.J. et al. (1987), "Evidence for neuromelanin involvement in MPTP-induced neurotoxicity," *Nature* 327:324-326 (of record), correlated protection of monkeys from motor effects of MPTP administration with plasma levels of pre-administered chloroquine. Golden, G.T., "Systemic Chloroquine Protects Against Striatal Dopamine Depletion Induced by Unilateral Intra-Nigral MPP Injection in Rats," (Abstract of talk before Society for Neuroscience, 1992, believed unpublished) (of record) disclosed that ip administration of chloroquine reduced dopamine depletion in rat brains subsequently injected with MPP+. (MPP+ administered to healthy animals mimics symptoms of Parkinson's.)

Since the art teaches that systemic levels of chloroquine correlate with desirable effects in the brain when challenged with MPP+, one skilled in the art would be motivated not to administer a brain-targeting agent (which would reduce systemic chloroquine levels).

Increasing brain choroquine levels after an ischemic event leads to severe nitric oxide damage. As shown in the Stranahan Declaration submitted herewith, shortly after an ischemic event, a cascade is initiated which causes nitric oxide damage to brain cells when chloroquine is administered. Treatment of such events normally occurs after this cascade is well underway. Treatment with chloroquine compounds in accordance with normal timing for treatment would therefore cause severe nitric oxide damage to brain cells. Thus, one skilled in the art would be motivated to not administer chloroquine, and certainly not to increase brain damage by increasing the amount of choroquine in the brain with a targeting agent. [Note that in Parkinson's this cascade resulting in nitric oxide damage is not initiated, and therefore is not exacerbated by administration of chloroquine.]

For all the foregoing reasons, one of skill in the art would not be motivated to combine a targeting agent with chloroquine compound. In fact, one of skill in the art would be motivated to *avoid* such a combination. Thus, no *prima facie* case of obviousness has been, or can be, made out, and it is respectfully submitted that the rejections under Section 103 be withdrawn.

The Rejection Under Section 103(a) Over Bussey, Lim et al. and Di Rocco, et al.

Claims 1-13 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Bussy, R. K., Editor-in-Chief, Merritt's Textbook of Neurology, Ninth Edition, pages 713-730 in view of Lim, L. Y. et al. of Clinical and Experimental Pharmacology & Physiology 12, 527-531, 1985 in further view of Di Rocco et al. of U.S. Patent No. 5,496,836. The Office Action states:

> Bussy, R. K. teach of treating parkinsonian syndromes, namely Parkinson's Disease and drug-induced Parkinsonism, which are movement disorders, (see page 713-716 and 727-730). In addition, Bussy, R. K. teach of various therapeutic treatments for Parkinson Disease, namely anticholinergics, antihistamines, and antidepressants, including serotonin-uptake inhibitors, (see page 722), which provides the skilled artisan with motivation to utilize various types of compounds to treat parkinsonian syndromes, namely Parkinson's Disease and drug-induced Parkinsonism. Lim et al. teach that compounds possessing the quinoline nucleus, including chloroquine, have long been associated with anticholinergic activity, (see page 527). Moreover, Lim, L. Y. et al. provide the skilled artisan with the notion that compounds possessing the quinoline nucleus, including chloroquine, have long been associated with anticholinergic activity. Di Rocco et al. teach of treating movement disorders, such as Parkinson's Disease, with the administration of cimetidine, (see column 5, lines 20-45 and from column 6, line 23 to column 7, line 11). It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Moreover, it is well within the

> level of the skilled artisan to determine optimal modes and methods of administration as well as the procedures for making pharmaceutical compositions having the optimum therapeutic dosage while minimizing adverse and/or unwanted side effects.

This rejection is respectfully traversed. Lim et al. show that chloroquine and related compounds inhibit acetylcholinesterase. It does not teach that these compounds are associated with anticholinergic activity. In fact the teachings of Lim et al. would lead one to believe that chloroquine and related compounds were **not** associated with anticholinergic activity. An acetylcholinesterase inhibitor is, as defined in the art is:

> Acetylcholinesterase inhibitors (AChEIs): A class of drugs that block the action of the acetylcholinesterase enzyme in the synaptic cleft, **therefore increasing the level of acetylcholine in the brain.**" [Emphasis added.]

Anticholinergic activity is defined as:

> Anticholinergic drugs: A group of drugs that **block** the effects of acetylcholine on nerve cells. [Emphasis added.]

These definitions are taken from the following website:
http://www.dementia.com/gldisplay.jhtml?itemname=d_glossary#gl_AChEIs. A copy of the relevant portion of the website is attached as Exhibit N with the above definitions highlighted.

By showing that chloroquine compounds are inhibitors of acetylcholinesterase, Lim et al. show that they increase the level of acetylcholine in the brain. This would obviously have exactly the opposite effect of a drug that **blocks** the effects of acetylcholine on nerve cells (an anticholinergic drug). Therefore, the Lim et al. reference teaches away from the use of chloroquine as an anticholinergic.

Moreover, Bussy teaches only that certain anticholinergics have been used as treatments for Parkinson's Disease, namely trihexyphenidyl, benztropine, ethopropazine, biperiden, cycrimine, and procyclidine. It does not teach that any

anticholinergic drug is useful as a treatment for Parkinson's Disease, nor that chloroquine is an anticholinergic drug. When combined with Lim et al., the references teach away from the use of chloroquine compounds to treat Parkinson's Disease.

It is well-settled that a reference that teaches against a claimed element cannot be used to formulate an obviousness rejection. (See, *e.g., Mitsubishi Elec. Corp. v. Ampex Corp.* 190 F.3d 1300, 51 U.S.P.Q.2d 1910 (CAFC 1999).) Moreover, there is no motivation to combine the references. Thus no *prima facie* case of obviousness has been made out.

Moreover, as shown above with respect to the rejection based on Roberts-Lewis et al. and Di Rocco et al., the alleged Di Rocco teaching that cimetidine is useful as a treatment for Parkinson's Disease, taken in light of the file history of the patent in which it occurs, turns out not to be credible. Thus this reference would not be relied upon by one skilled in the art as a suggestion that cimetidine would be useful in the treatment of Parkinson's Disease. In fact, cimetidine is not used as a treatment for Parkinson's Disease *per se* in the present invention. Rather, as claimed, it is used as a peripheral metabolism inhibitor of the chloroquine compound so that more of the chloroquine compound reaches the brain.

Furthermore, in view of the state of the art, one skilled in the art would not be motivated to administer chloroquine and cimetidine simultaneously. Submitted as Exhibit O hereto is a printout from the drug interaction database of MicroMedEx downloaded on December 20, 2005, showing that concurrent use of the combination of chloroquine and cimetidine is contraindicated based on documentation rated "GOOD" and showing a severity rated "MAJOR." This combination can result in agitation seizures and cardiac arrest. [See the entry bridging pages 2 and 3 of the printout.]

Based on this clear teaching against concurrent administration of chloroquine and cimetidine in the literature, it is submitted that one skilled in the art would not be led by the cited references to combine these compounds. Thus no *prima facie* case of obviousness can be made out. (Applicant combines these compounds using lower dosages of both than taught in the art for administration of either compound. Specifically, the cimetidine dosages taught in the Di Rocco patent would be toxic, and would be likely to *cause* movement disorders. Applicant uses cimetidine to increase the bioavailability of chloroquine to the melanized neurons in the brain, and not directly as a therapeutic agent.)

It is therefore submitted that no *prima facie* case of obviousness has been made out, and that even if it had been, the references when combined do not teach the present invention. Withdrawal of the rejection is therefore respectfully requested.

The Double Patenting Rejection

The claims have been provisionally rejected for nonstatutory double patenting over the claims of Serial No. 10/192,414. The Office Action states that a timely filed terminal disclaimer in compliance with 37 CFR 1.321 (c) may be used to overcome the rejection under 37 CFR 1.130(b). A Terminal Disclaimer is submitted herewith, thus overcoming the rejection.

Conclusion

This application appearing to be in condition for allowance, passage to issuance is respectfully requested. Exhibits A-O, a Terminal Disclaimer, a PTO/SB-96, and a Petition for Extension of Time of three months is submitted herewith, along with a substitute SB-08a form and legible copies of references lined out on the Form PTO 1449 received with the Office Action.

Please deduct all fees required including fees for further extensions of time if needed, from deposit account 07-1969.

Respectfully submitted,

Ellen P. Winner

Ellen P. Winner
Reg. No. 28,547

GREENLEE, WINNER AND SULLIVAN, P.C.
4875 Pearl East Circle, Second Floor
Boulder, CO 80301
Telephone: (303) 499-8080
Facsimile: (303) 499-8089
E-mail: winner@greenwin.com

Attorney docket No. 47-00B
September 1, 2006

Exh A

Claims

1. A method for inhibiting neuronal cell death in a mammal resulting from a disorder of the central or peripheral nervous system comprising administering to said mammal a neuronal cell death inhibitng amount of a preparation comprising any of mepacrine, chloroquine, or hydroxychloroquine, said preparation being essentially free of colchicine.

2. The method of claim 1, wherein said cell death is the result of a calcium related disorder.

3. The method of claim 1, wherein said disorder is Alzheimer's disease.

4. The method of claim 1, wherein said disorder is any of stroke ischemia, anoxia, hypoxia, or hypoglycemia.

5. The method of claim 1, wherein said disorder is any of Parkinson's disease, Huntington's disease, AIDS dementia, epilepsy, motor neuron diseases, peripheral nerve degeneration, or head or spinal cord injuries.

6. The method of claim 1, wherein said cell death occurs in the hippocampus.

7. The method of claim 1, wherein said cell death occurs at a cholinergic neuron.

8. The method of claim 1, wherein said cell death occurs in the substantia nigra.

Sub C2 cont

9. The method of claim 1, wherein said cell death occurs at a dopaminergic neuron.

10. The method of claim 1, wherein said cell death occurs in the basal ganglia.

11. The method of claim 1, wherein said cell death occurs at a neuron that comprises a nerve growth factor receptor.

12. The method of claim 1, wherein said cell death occurs in the spinal cord.

13. The method of claim 1, wherein said cell death occurs at a motor neuron.

14. The method of claim 1, wherein said cell death occurs at a GABAergic neuron.

15. The method of claim 1, wherein said cell death occurs in a subcortical neuron.

16. The method of claim 1, wherein said cell death occurs in the ventral forebrain.

17. The method of claim 1, further comprising administering to said mammal a neuronal cell death inhbiting amount of a compound which blocks excitatory amino acid actions or calcium channel activity.

18. The method of claim 17, wherein said compound comprises any of flunarizine, verapamil, nimodipine, or nifedipine.

19. The method of claim 17, wherein said compound comprises an antagonist to any of an excitatory amino acid receptor, an angiotensin II receptor, or a bradykinin receptor.

20. The method of claim 1, wherein said preparation is administered after the onset of said disorder.

21. The method of claim 1, wherein said preparation is administered within one hour of the onset of said disorder.

22. The method of claim 1, wherein said cell death occurs at a cell that has been subjected to ischemia, hypoxia, anoxia, or hypoglycemia.

23. A method of inhibiting non-neural cell death from ischemia in a mammal comprising administering to said mammal a cell death inhibiting amount of a preparation comprising any of mepacrine, chloroquine, or hydroxychloroquine.

24. The method of claim 23, wherein said preparation is essentially free of colchicine.

25. The method of claim 23, wherein said cell death occurs in muscle tissue.

26. The method of claim 23, wherein said cell death occurs in smooth muscle tissue.

27. The method of claim 23, wherein said cell death occurs in cardiac tissue.

28. The method of claim 1, wherein said cell death occurs in the cortex.

Add B3

Add C5

Exh
B

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/838,598	02/19/92	ROBERTS-LEWIS	02655/002002 SAH

PAUL T. CLARK
FISH & RICHARDSON
225 FRANKLIN STREET
BOSTON, MA 02110-2804

EXAMINER		
TRAVERS, R		
ART UNIT	PAPER NUMBER	
1205	3	
DATE MAILED:	09/11/92	

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on ____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ ____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-28 are pending in the application.
   Of the above, claims 17-22 are withdrawn from consideration
2. ☐ Claims ____ have been cancelled.
3. ☐ Claims ____ are allowed.
4. ☒ Claims 1-16 + 23-28 are rejected.
5. ☐ Claims ____ are objected to.
6. ☐ Claims ____ are subject to restriction or election requirement
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on ____ Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on ____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on ____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. ____ ; filed on ____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

PTOL-326 (Rev. 9-89) EXAMINER'S ACTION

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-16 and 23-28, drawn to compositions inhibiting neural cell death and method of using said compositions.

II. Claims 18-22, drawn to a combination of the active ingredients of group I and Calcium channel blockers to prevent neural cell death.

III. Claims 18-22, drawn to a combination of the active ingredients of group I and compounds effective in blocking the binding sites of neurologically active amino acid analogues to prevent neural cell death.

During a telephone conversation with Paul T. Clark on August 5, 1991 a provisional election was made with traverse to prosecute the invention of group I, claims 1-16 and 23-28. Affirmation of this election must be made by applicant in responding to this Office action. Claims 17-22 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1-16 are rejected under 35 U.S.C. § 101 because the invention as disclosed is inoperative and therefore lacks

utility.

The claims set forth numerous conditions treatable with the instant compositions, but fails to show such treatments as effective against the maladies set forth in the instant claims.

OK argue cause + Effect

Claims 1 and 6-16 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to treatment of various necrotic conditions. See M.P.E.P. §§ 706.03(n) and 706.03(z).

OK

Claims 1-16 and 23-28 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-16 and 23-28 are rendered indefinite for failing to indicate if the methods are intended to treat or prevent the enumerated conditions.

OK

Claims 2 and 5 are rendered indefinite for failing to specifically set forth the conditions and/or maladies treated. Claims 2 and 5 are directed to the treatment of "calcium related disorder", "motor neuron diseases", Peripheral nerve degradation, or head or spinal cord injuries" and as such fail to specifically set forth the embodiments of the instant claims.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section

102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-16 and 23-28 are rejected under 35 U.S.C. § 103 as being unpatentable over Rosner et al, Jun et al and Larson et al in view of Molnor et al and Effland et al, all of record.

Rosner et al teach the beneficial activity of the claim designated compounds in preventing and treating ischemic damage. Jun et al teach the reduction of oxygen consumption in damaged neurological tissue treated with the claim designated active ingredients. Larson et al teach the claim designated active ingredients capacity to protect against damage due to ischemic neurological disorders. The skilled artisan would have been motivated to employ the instant anti-ischemic compounds for the neural conditions herein claimed. it would follow therefore that the subject matter herein claimed would have been <u>obvious</u> to the skilled artisan and is properly rejected under 35 USC 103.

Applicant has not argued that the claimed proportioning and/or dosage amounts add patentable moment to the recited claims.

Thus the only issue presented in the instant application is the obviousness of using the claim designated composition for an old and well known utility.

NO claims are allowed.

Any inquiry concerning this communication should be directed to Russell Travers at telephone number (703) 308-4603.

Frederick E. Waddell
Supervisory Patent Examiner
Group 120

P.1

Exh. C

[Drug-induced movement disorders] Takahashi A; Murasaki M Department of Psychiatry, Kitasato University School of Medicine. Nippon rinsho (JAPAN) Nov 1993, 51 (11) p2929-34, ISSN 0047-1852 Journal Code: KIM Languages: JAPANESE Document type: Journal Article; Review; Review, Tutorial Record type: Completed Subfile: INDEX MEDICUS Many drugs have been known to cause movement disorders with different mechanisms of action. Most of these drugs interfere with dopaminergic transmission within the basal ganglia. However, numerous other drugs are capable of producing movement disorders, whose mechanism is not at all clearly understood. Neuroleptic drugs-induced extrapyramidal symptoms such as dystonia, akathisia, parkinsonism have been related to sudden imbalance between the striatal dopamine and cholinergic systems, causing a relative preponderance of acetylcholine. Some calcium channel blockers and H2 blockers induced or aggravated parkinsonism and other extrapyramidal symptoms. It has been suggested that calcium channel blockers-induced extrapyramidal symptoms are much more common in elderly patients. In H2 blockers induced movement disorders, renal and liver dysfunction is the risk factor of them, but the mechanism is not clearly understood.

Cinnarizine-induced parkinsonism in primates. Garcia Ruiz PJ; Mena MA; Penafiel N; De Yebenes JG Department of Neurology, Fundacion Jimenez Diaz, Madrid, Spain. Clinical neuropharmacology (UNITED STATES) Apr 1992, 15 (2) p152-4, ISSN 0362-5664 Journal Code: CNK Languages: ENGLISH Document type: Journal Article Record type: Completed Subfile: INDEX MEDICUS We describe the production of an experimental model of parkinsonism induced by cinnarizine (CNZ) in three healthy sylvanna monkeys. The drug produced a severe but reversible parkinsonism in all animals. After discontinuation of CNZ, all animals recovered but the oldest one was akinetic for 6 weeks. CNZ produced a persistent reduction in HVA and 5-HIAA levels in the CSF. Our data suggest a predominant presynaptic effect on DA and 5-HT neurons; and could account for the longstanding parkinsonism induced by calcium antagonist in some patients as well as the depression observed in these subjects.

Parkinsonism associated with calcium channel blockers: a prospective follow-up study. Garcia-Ruiz PJ; Garcia de Yebenes J; Jimenez-Jimenez FJ; Vazquez A; Garcia Urra D; Morales B Department of Neurology, Hospital Universitario San Carlos, Madrid, Spain. Clinical neuropharmacology (UNITED STATES) Feb 1992, 15 (1) p19-26, ISSN 0362-5664 Journal Code: CNK Languages: ENGLISH Document type: Journal Article Record type: Completed Subfile: INDEX MEDICUS Parkinsonism is a well-known side effect of some calcium channel blockers (CCB). Its long-term evolution, however, is unknown. To clarify this issue, we performed a prospective follow-up study involving 32 patients diagnosed with CCB-induced parkinsonism. After the baseline examination, the CCB were discontinued and serial evaluations were carried out according to the same protocol. Despite a global improvement, cognitive and mood disturbances subsided slowly, and tremor persisted in most patients. After 18 months of CCB withdrawal, 44% of patients had depression, 88% had tremor, and 33% still had criteria for

(Exhibit C p. 2

diagnosis of parkinsonism. During the survey, only three patients were found to be fully recovered. The improvement of some clinical symptoms was related to age: Patients younger than 73 years recovered better than older patients did. Our data indicate that CCB-induced parkinsonism is not the benign condition previously thought, and suggest an age-related prognosis of this entity.

Calcium-entry blockers-induced parkinsonism: possible role of inherited susceptibility. Negrotti A; Calzetti S; Sasso E Istituto di Neurologia, Universita di Parma, Italy. Neurotoxicology (UNITED STATES) Spring 1992, 13 (1) p261-4, ISSN 0161-813X Journal Code: OAP Languages: ENGLISH Document type: Journal Article Record type: Completed Subfile: INDEX MEDICUS The risk of developing drug-induced parkinsonism (DIP) has been related to a number of factors but it remains up to now poorly defined. The aim of this survey has been to evaluate retrospectively the possible role of inherited components in 25 patients with parkinsonism induced by chronic exposure to the calcium-entry blockers cinnarizine and flunarizine. The finding of higher occurrence of a positive family history for Parkinson's disease (PD) and/or essential tremor (ET) and of higher frequency of secondary cases with PD and/or ET among close relatives of the patients as compared to age-matched controls, suggests the involvement of genetic susceptibility in developing this drug-induced disorder. DIP could be regarded as a multifactorial disease process resulting from potential neurotoxicity of drugs on a background of inherited predisposition.

[Parkinsonism, depression and akathisia induced by flunarizine, a calcium entry blockade--report of 31 cases] Kuzuhara S; Kohara N; Ohkawa Y; Fuse S; Yamanouchi H Rinsho shinkeigaku (JAPAN) Jun 1989, 29 (6) p681-6, ISSN 0009-918X Journal Code: DF2 Languages: JAPANESE Document type: Journal Article Record type: Completed Subfile: INDEX MEDICUS Flunarizine hydrochloride (FZ), a calcium entry blockade, has been used nationwide in Japan as a cerebral active vasodilator since October, 1984. The present paper reports 31 cases of FZ-induced Parkinsonism, depression and akathisia, referred to our hospital between October 1986 and September 1988. Out of the 31 patients, four including two with Parkinson's disease and one each with progressive supranuclear palsy and olivopontocerebellar atrophy showed worsening of their parkinsonian symptoms within a few months after FZ administration. The remaining 27 patients (7 males and 20 females) newly developed Parkinsonism after treatment with FZ. Symptoms appeared one week to two years (mean: 6.1 months) after starting FZ of a daily dose of 10 mg. FZ had been used in 6 patients for cerebrovascular episodes confirmed by clinical history or brain CT, and in the remainder, for dizziness, light-headedness, hypertension, amnesia or hypochondric neurotic complaints. Akinesia and bradykinesia progressed rather rapidly after onset, and patients became unambulatory within several months. Symptoms had worsened, and L-dopa, anticholinergic drugs, and bromocriptine had been ineffective until FZ was discontinued. Their Parkinsonism was characterized by marked akinesia, bradykinesia, and moderate rigidity. Masked face was seen in most of them. Tremor was absent at rest, and induced in 12 patients by posture and/or action. Sixteen patients were accompanied by depression, and five, by akathisia. Improvement began several weeks after withdrawal of FZ, and most patients recovered almost completely within a few months although mild rigidity and bradykinesia remained in

Exhibit C p.3

some.(ABSTRACT TRUNCATED AT 250 WORDS)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Exh D

In re Application of:

Nelson, J. Group: 1614

Serial No. 09/615,639 Examiner: Sarada Prasad

Filed: July 13, 2000

For: COMPOSITIONS AND METHODS FOR THE TREATMENT OF PARKINSON'S DISEASE

DECLARATION OF PATRICIA L. STRANAHAN, M.D., Ph.D.

I, Patricia L. Stranahan, M.D., Ph.D. state as follows:

I am Medical Director of Alpha Research Group, and have been employed in that position since March 22, 2000. I am presently Professor of Pathology at Ross University School of Medicine, having recently accepted this appointment last year (2001). Prior to this appointment, I served as Professor and the Chair of the Department of Biology at Metropolitan State College of Denver (1988-2000). I have held both Regular and Adjunct Fellow/Assistant Professorships at the University of Colorado Health Sciences Center where I taught Pathology, Physiology and Biophysics, Histology and Pathophysiology (1985-1999). Prior to becoming a Professor of Pathology, I served as a Pathologist in both military and civilian capacities (1978-1984). I am double board certified in Pathology, both Anatomic and Clinical (ASCP). I am Board eligible (ASCP) in Blood Banking and Hematopathology. A copy of my curriculum vitae is attached hereto.

I have reviewed Patent No. 5,430,039 and the claims pending in the above-captioned application. It is my opinion that the pending claims are not obvious in view of the said patent because the '039 patent does not enable one skilled in the art of medicine to treat an ischemic event (stroke, CVA) using chloroquine. In fact, '039 describes a treatment approach that would be detrimental to administer following the incidence of ischemia, neuronal or otherwise, by persons skilled in the art and knowledgeable in the pathological cascades precipitated by ischemic events for the following reasons:

As is known to the art, cerebral ischemia immediately triggers an inflammatory cascade in which cytokines, tumor necrosis factor alpha (TNF-α) and interleukins (IL), the most relevant to the topic at hand being IL-6, are released. TNF and IL-6 degrade inhibitor κB-α (I-κB-α), which prevents the activation of nuclear factor κB (NF-κB). Once activated, NF-κB migrates to the

nucleus and augments mRNA synthesis of other "mediator compounds" that contribute to and/or participate in the body's inflammatory response. One such "mediator" that is produced by NF-κB activation is inducible nitric oxide synthase (iNOS), which increases nitric oxide and nitrite oxide (NO and NO_2, respectively) formation in ischemic tissues. Furthermore, NF-kappa-B activation augments the production of other reactive oxygen species, such as superoxide radical formation (O_2^-). Oxygen free radicals combine with the newly formed and abundantly available reactive nitrogen intermediates (i.e.-·NO and NO_2) to generate peroxynitrite ($ONOO^-$), which results in extensive neural damage following an ischemic event. Any cell producing high levels of NO and/or $ONOO^-$ will inhibit its own respiration and that of surrounding cells (see, e.g. Brown, G. and Borutaite, V., (2000), "Nitric oxide, cytochrome c and mitochondria," Biochemical Society Symposium 66:17-25).

The tissue damage is exacerbated when reperfusion injuries occur (as happens in 50% of cases of ischemia, as discussed above), because reperfusion results in surges of NO and O_2^- generation, to produce $ONOO^-$ which mediates a predominant amount of reperfusion damage.

After NF-κB has unregulated the synthesis of the inflammatory response mediators, it eventually induces the synthesis of mRNA required to produce the inhibitor molecule I-κB-α. Once I-κB-α is then re-synthesized, it binds directly to and inhibits NF-κB. The inflammatory response and production of reactive species will then begin to damp down, however, generally not before a great deal of neural damage has been done. See Trajkovic, V., et al. (2001, "Amphotericin B potentiates the activation of inducible nitric oxide synthase and causes nitric oxide-dependent mitochondrial dysfunction in cytokine-treated rodent astrocytes," GLIA 35(3):180-188; Ichiyama, T. et al. (2001), "Thiopental inhibits NF-kappaB activation in human glioma cells and experimental brain inflammation," Brain Research 911(1):56-61; Jarosinski, K.W., et al. (2001), "Specific deficiency in nuclear factor-kappaB activation in neurons of the central nervous system," Laboratory Investigation 81(9):1275-1288; Sekine, N. et al. (2001), "GH inhibits interferon-gamma-induced signal transducer and activator of transcription-1 activation and expression of the inducible isoform of nitric oxide synthase in INS-1 cells," Endocrinology 142(9):3909-3916; and Ganster, R.W., et al. (2001), "Complex regulation of human inducible nitric oxide synthase gene transcription by Stat 1 and NF-kappa B," PNAS US 98(15):8638-8643).

It is well known to those skilled in the art that chloroquine is a potent inhibitor of both TNF-α and IL-6. See Park, Y.C., et al. (1999), "Chloroquine inhibits inducible nitric oxide synthase expression in murine peritoneal macrophages," Pharmacology & Toxicology 85(4):188-191;Weber, S.M. and Levitz, S.M. (2000), "Chloroquine interferes with lipopolysaccharide-induced TNF-alpha gene expression by a nonlysosomotropic mechanism," Journal of Immunology 165(3):534-1540; Harabak, A. et al. (1998), "Action of chloroquine on nitric oxide production and parasite killing by macrophages," European Journal of Pharmacology 354(1):83-90. In that both TNF-α and IL-6 "initiate" the inflammatory cascade by degrading the NF-κB inhibitor compound, I-κB-α, it is reasonable to assume that chloroquine and similar agents do in fact possess neural protective properties suitable to be employed for ischemia and other noxious

events—which is exactly what patent '039 demonstrates. However, the teachings of this patent do not enable one skilled in the art to use chloroquine to treat an ischemic event in a patient.

Examples in the '039 patent show treatment of brain tissue with mepacrine *prior to or at the time of* damaging the tissue with kainate or tying off blood vessels to simulate cerebral ischemia (the patent asserts that chloroquine can be substituted for mepacrine). See col. 3, line 67 through col. 4, line 2: "In FIG. 1 cannulated rats received 160 nmol of mepacrine (cross hatched bar), or vehicle (solid bar), by icv infusion, 10 minutes *prior* to and 3 hours following icv infusion of kainic acid." See also col. 4, lines 11-14: "In FIG. 2 cannulated rats received 160 nmol of mepacrine (cross-hatched bar), or vehicle (solid bar), by icv infusion, immediately prior to icv infusion of kainic acid." At col. 6, lines 59-63: "As shown in FIG. 7, gerbils received mepacrine (80 mg/kg, ip) (cross hatched bar), or vehicle (control) (solid bar), *immediately prior to* and once a day (40 mg/kg, ip) for 6 days after bilateral occlusion of the carotid arteries." When spectrin breakdown was stimulated by NMDA, mepacrine and chloroquine were co-administered with NMDA or administered immediately afterward (col. 6, lines 1-21). After traumatic transection of the fimbria-fornix, mepacrine was administered mepacrine *at the time of* transection.

Thus, as is demonstrated in '039, if administered prior to the beginning of the cytokine cascade initiated by a cerebral ischemic event, chloroquine prevents degradation of I-κB-α, which inhibits NF-κB and prevents formation of the reactive species that are so damaging to neurons.

However, if chloroquine is administered after the ischemic event, when cytokine production has been initiated (which happens immediately) it prevents synthesis of I-κB-α, thus allowing for enhanced, unchecked, prolonged activation of NF-κB, which would serve to enhance production of damaging reactive species. Thus, when administered following the initiation of the inflammatory cascade, chloroquine soon potentiates the availability of noxious oxygenated and nitrogen radical species, which then in turn potentiate the release of excitatory neurotransmitters (i.e.- glutamate) and promote NMDA receptor stimulation that both mediate increased NO generation. See, e.g. Eliasson, M.J.L., et al. (1999), "Neuronal Nitric Oxide Synthase Activation and Peroxynitrite Formation in Ischemic Stroke Linked to Neural Damage," Journal of Neuroscience 19(14):5910-5918; and Ghigo, D., et al. (1998), "Chloroquine stimulates nitric oxide synthesis in murine, porcine and human endothelial cells," Journal of Clinical Investigation 102(3): 595-605.

This cyclic generation of damaging species is termed a cytotoxic cascade, which can be precipitated by an ischemic event. If chloroquine is administered following the initiation of the inflammatory response, the promotion of the cytotoxic cascade is potentiated because research shows that I-κB-α is completely degraded within 15 minutes after a noxious event, and chloroquine administration prevents I-κB-α resynthesis. See Chen, F. et al. (1997), "Calpain contributes to silica-induced I kappa B-alpha degradation and nuclear factor-kappa B activation," Archives of Biochemistry & Biophysics 342(2):383-388.

The primary deficit of the '039 patent in failing to enablingly teach one skilled in the art to treat cerebral ischemia with chloroquine, is that one skilled in the art is aware of the impossibility

of administering neuroprotective agents *prior to*, *immediately prior to* and/or *at the time of* an ischemic event. Pretreating patients for cerebral ischemia is not possible, because these events are unpredictable. Treating patients for cerebral ischemia within less than about ten to fifteen minutes after the event is also not possible because typically patients have not reached a treatment facility within such a short period of time. It is well recognized in the art that in cerebral ischemia, treatment is not undertaken until at least about 6 to about 24 hours after the event. See, e.g., Conference Proceedings, "Stroke Drug Development: Bridging the Gap from Animal Research to Human Trials," March 6-7, 1999, Orlando, Florida, p. 49.

Thus, the only way chloroquine could function as an effective treatment for cerebral ischemia would be to administer it *before* the event, or within about ten to fifteen minutes after the event, i.e. before production of cytokines, TNF-alpha and IL-6 begins. From this it can be seen that when chloroquine is administered before the event, as in the '039 patent, it will prevent neural damage by preventing TNF alpha and IL-6 degradation of I-κB-α. Further it can be seen that administration of more chloroquine after the event and after the patient has been pretreated, as is demonstrated in some of the examples in the '039 patent, will not have any further effect because although it prevents synthesis of more I-κB-α, more I-κB-α is not needed because chloroquine has effectively inhibited the degradation of the I-κB-α which continues to effectively bind to and prevent the activation of inflammatory response activator nuclear factor NF-κB.

To summarize, given before an ischemic event, chloroquine can prevent neural damage. However, the art as a whole teaches that administration of chloroquine for treatment of cerebral ischemia after the first ten minutes will damage the neurons through increased nitric oxide and oxygenated radical production rather than having a protective effect. Subsequently, chloroquine given after an ischemic event would *enhance* neural damage. Therefore the teachings of patent '039 do not enable one skilled in the art, who is aware of the foregoing harmful effects of chloroquine, to treat cerebral ischemia using chloroquine.

Another important reason why the '039 patent fails to enablingly teach the use of chloroquine to treat cerebral ischemia to those skilled in the art of treating ischemia and/or those skilled in the art of administering emergency medical treatment is that those of skill in these arts are aware that chloroquine, administered iv, as is described in the '039 patent, results in cardiovascular toxicity and hypotension. See Scott, V. (1995), "Single intravenous injections of chloroquine in the treatment of falciparum malaria: toxic and immediate therapeutic effects in 11 cases," American Journal of Tropical Medicine and Hygiene 30:701-705; Laing, A. (1955), "The single dose treatment of falciparum malaria with Nivaquine: a review of 164 cases treated at the district hospital Kuala Langsar," Medical Journal of Malaya 9:216-221; Don-Michael, T. and Aiwazzadeh, S. (1970), "The effects of acute chloroquine poisoning with special reference to the heart," American Heart Journal 79:831-842; Sofola, O. (1980) "The cardiovascular affect of chloroquine in anesthetized dogs," Canadian Journal of Physiological Pharmacology 58:836-841. Persons who are skilled in the art of treating a suspected and/or confirmed victim of cerebral ischemia would not administer an agent (such as both the drug and method of drug delivery described in '039), that has a potential to induce cardiovascular toxicity and/or hypotension. It is well known to those skilled in the art of treating cerebral ischemia, that hypotension worsens a

stroke victim's prognosis and that agents capable of inducing a hypotensive state are contraindicated for use in patients who are experiencing an ischemic event.

Further, chloroquine is well known to the art to induce neurological and psychiatric effects such as hallucinations (see, e.g., Physician's Desk Reference, 2000, of record. Medical personnel who treat cerebral ischemia would not consider it reasonable to administer an agent capable of confounding a proper diagnosis by promoting the generation of neurological disturbances or stimulating psychiatric effects, such as are known to occur following chloroquine administration. Again, the '039 patent does not enablingly teach the use of chloroquine for cerebral ischemia to those of skill in the art because such a drug would be contraindicated, especially in cases where a valid neurological evaluation is required to accurately assess the severity of the ischemic event suffered.

The final reason why the '039 patent fails to teach those skilled in the art to use chloroquine to treat ischemia is that the '039 patent employs a defective study design and poor animal models for the experiments they claim demonstrate neuroprotection. Persons skilled in the art of stroke drug development would perceive little, if any, validity in the '039 patent's inference that these drugs would provide neuroprotection to humans who were faced with similar cerebral assaults as the rodents used in the '039 experiments. Several of the more obvious deviations from proper stroke drug development study design, as they appear in the methods discussions in '039, are presented below.

Neural damage, e.g. resulting from a five-minute occlusion, would not be expected to show up until about 7-28 days after cutting off blood flow. See Conference Proceedings, "Stroke Drug Development: Bridging the Gap from Animal Research to Human Trials," March 6-7, 1999, Orlando, Florida, and p. 28. However, in the '039 patent, results were evaluated only 24 hours after the event in rats and 4 to 6 days after the event in gerbils, while the art teaches that neural protective effects seen earlier tend to evaporate – indicating a mere postponement of injury rather than real protection.

Further, rats and gerbils, the animals in which results in the '039 patent were generated, are not good animal models for cerebral ischemia in humans. Gerbils are notorious for false positive results in studies involving neural protection (see Feuerstein, G.Z. and Wang, X (2000), "Animal models of stroke," Molecular Medicine Today 6(March):133-135), and both rats and gerbils are poor models for cerebral ischemia because repercussion injury (which occurs in humans by 24 hours, at about 50%) does not occur in rodents (see Conference Proceedings, "Stroke Drug Development: Bridging the Gap from Animal Research to Human Trials," March 6-7, 1999, Orlando, Florida, pp 20-21). See also, Cockcroft, KM, et al. (1996), "Cerebroprotective Effects of Aminoguanidine in a Rodent Model of Stroke," Stroke 27(8):1393-1398 and Editorial Comment by G. Feuerstein, M.D. at p. 1398, which indicates that a neural protective effect appearing two hours after ischemia did not occur three hours after ischemia.

Moreover, it is my opinion that the patent does not teach or suggest the use of targeting agents with chloroquine for any purpose. A targeting agent would increase the amount of chloroquine reaching the brain, which would intensify the harmful effects discussed above.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Patricia L. Strunahan MD, PhD
Patricia L. Strunahan, M.D.Ph.D.

Date: Jan. 14, 2002

Exh E

Ellen Winner

From: jodi nelson [jodi_n@comcast.net]
Sent: Saturday, November 26, 2005 8:57 AM
To: Ellen Winner
Subject: citation FAMO 40-6-xs more potent

http://0-www.thomsonhc.com.library.uchsc.edu/hcs/librarian/ND_PR/Main/SBK/2/PFPUI/NG4m3Qm13zWjXV

4. Mechanism of Action / Pharmacology

A. MECHANISM OF ACTION

1. SUMMARY

a. Famotidine is an H2-antagonist effective in suppressing basal, nocturnal, pentagastrin, and meal-stimulated acid secretion (Ryan, 1984; Ohe et al, 1984; Muller et al, 1984; (McCallum et al, 1983). Acid secretion secondary to histamine or tetragastrin release is also inhibited by famotidine (Ohe et al, 1984). The onset of activity generally begins within 1 to 2 hours after drug administration, peaks at 1 to 3 hours, and maintains acid suppression for 10 to 12 hours. The duration of activity can persist up to 18 to 24 hours at higher doses of 40 to 80 mg (Smith, 1985). The anti-secretory activity of famotidine has been reported to be 40 to 60 times more potent than cimetidine and 12 to 15 times more potent than ranitidine on a milligram per milligram basis (Smith, 1985). Peptic ulcer disease that may be secondary to Campylobacter pylori infection will not be affected by famotidine treatment. Alcohol use, ulcer size, bleeding symptoms, a previous duodenal ulcer, and previous use of salicylates or nonsteroidal anti- inflammatories independently influence healing rate of ulcers at 4 weeks (Reynolds et al, 1994). Later studies showed that smoking, ulcer size and multiple ulcers are also risk factors for delayed healing. Multiple risk factors also increase healing time (Reynolds et al, 1994).

4.4. Mechanism of Action / Pharmacology

A. MECHANISM OF ACTION

1. SUMMARY

a. Famotidine is an H2-antagonist effective in suppressing basal, nocturnal, pentagastrin, and meal-stimulated acid secretion (Ryan, 1984; Ohe et al, 1984; Muller et al, 1984; (McCallum et al, 1983). Acid secretion secondary to histamine or tetragastrin release is also inhibited by famotidine (Ohe et al, 1984). The onset of activity generally begins within 1 to 2 hours after drug administration, peaks at 1 to 3 hours, and maintains acid suppression for 10 to 12 hours. The duration of activity can persist up to 18 to 24 hours at higher doses of 40 to 80 mg (Smith, 1985). The anti-secretory activity of famotidine has been reported to be 40 to 60 times more potent than cimetidine and 12 to 15 times more potent than ranitidine on a milligram per milligram basis (Smith, 1985). Peptic ulcer disease that may be secondary to Campylobacter pylori infection will not be affected by famotidine treatment. Alcohol use, ulcer size, bleeding symptoms, a previous duodenal ulcer, and previous use of salicylates or nonsteroidal anti- inflammatories independently influence healing rate of ulcers at 4 weeks (Reynolds et al, 1994). Later studies showed that smoking, ulcer size and multiple ulcers are also risk factors for delayed healing. Multiple risk factors also increase healing time (Reynolds et al, 1994).

2. Famotidine (YM-11,170; MK-208) is an H2-receptor blocking agent which has been demonstrated to be a potent inhibitor of gastric acid secretion (Smith, 1985; Harada et al, 1983; Takeda et al, 1982a; Takagi et al, 1982; Tomioka & Yamada, 1982). The drug is an amidine derivative with the thiazole side chain (Takagi et al, 1982). The chemical name of famotidine is 3((2-(diaminomethylene)amino) 4-thiazolyl-methyl-thio)-N2-sulfamoyl propionamidine (Takagi et al, 1982). The empirical formula of famotidine is $C8H15N7O2S3$ and its molecular weight is 337.43 (Prod Info Pepcid(R), 1996b).

3. In man, famotidine has been effective in suppressing basal, nocturnal, pentagastrin- and meal-stimulated acid secretion (McCallum et al, 1983; Ryan, 1984; Ohe et al, 1984; Muller et al, 1984), as well as acid secretion secondary to histamine and tetragastrin (Ohe et al, 1984). The drug has been reported 40 to 60 times as potent as cimetidine and 12 to 15 times as potent as ranitidine (Smith, 1985). It is suggested that, compared to cimetidine or ranitidine, famotidine is unique in that it is a slowly reversible, competitive H2-receptor antagonist, dissociating slowly from the active site; dimaprat (an H2-agonist) was not able to overcome the H2-receptor blocking activity of famotidine, even with increasing concentrations of agonist (Smith, 1985; Pendleton et al, 1983).

4. The duration of action of famotidine is dose-related. Suppression of acid secretion has been observed for up to 12 hours with 20 mg oral doses and 18 to 24 hours with doses of 40 to 80 mg orally (Smith, 1985). Doses of 5 mg orally have suppressed pentagastrin-induced acid secretion (40% of the pentagastrin-simulated acid output) for 5 to 7 hours (Smith et al, 1985). The degree of acid suppression with famotidine in doses of 5 mg orally is similar to that observed with cimetidine 300 mg orally; higher doses of famotidine (10 and 20 mg) have produced greater acid suppression than 300 mg cimetidine (Smith, 1985). Famotidine 40 mg as a single nighttime dose was comparable to ranitidine 300 mg orally (but not bedtime cimetidine) in reducing 24-hour intragastric acidity (Dammann et al, 1983b; Dammann et al, 1984).

5. Famotidine 5 mg orally was comparable to 300 mg cimetidine in suppressing stimulated acid secretion in normal volunteers. Two hours following oral doses, acid secretion was suppressed to 60% of control with 5 mg famotidine and to 55% of control with 300 mg cimetidine. Higher doses of famotidine produced greater suppression of acid secretion (70% and 90% with 10 mg and 20 mg orally, respectively). Famotidine appears to be 30 to 60 times as potent as cimetidine on a weight basis and has a longer half life than either cimetidine or ranitidine, suggesting once daily dosing (Smith, 1985).

6. Animal studies have reported that famotidine does not influence the antigen-induced mediator release from mast cells or humoral and cell-mediated immune responses (Tomioka et al, 1983).

7. In man, famotidine has been effective in suppressing basal, nocturnal, pentagastrin- and meal-stimulated acid secretion (McCallum et al, 1983; Ryan, 1984; Ohe et al, 1984; Muller et al, 1984), as well as acid secretion secondary to histamine and tetragastrin (Ohe et al, 1984). The drug has been reported to be 40 to 60 times as potent as cimetidine and 12 to 15 times as potent as ranitidine (Smith, 1985). It is suggested that, compared to cimetidine or ranitidine, famotidine is unique in that it is a slowly reversible, competitive H2-receptor antagonist, dissociating slowly from the active site; dimaprat (an H2-agonist) was not able to overcome the H2-receptor blocking activity of famotidine, even with increasing concentrations of agonist (Smith, 1985; Pendleton et al, 1983).

B. REVIEW ARTICLES

1. The pharmacology and therapeutic utility of famotidine have been reviewed (Hatlebakk & Berstad, 1996; Dammann, 1990; Gitnick, 1989; Berardi et al, 1988; Friedman, 1987; Freston, 1987; Campoli-Richards & Clissold, 1986).

2. A review of the pharmacokinetics and drug interactions of famotidine have been provided (Echizen & Ishizaki, 1991a; Lauritsen et al, 1990; Sax, 1987).

Exh. 6

Topics:	Column One	Column Two
	CIMETIDINE	**FAMOTIDINE**
Details in DRUGDEX®	CIMETIDINE	FAMOTIDINE
Tradenames	• Tagamet • Tagamet HB See Complete Tradename Listing	• Pepcid • Pepcid AC • Heartburn Relief See Complete Tradename Listing
Class	• Antiulcer • Histamine H2 Antagonist	• Antiulcer • Histamine H2 Antagonist
Adult Dose	• Duodenal ulcer disease: active, 800 mg ORALLY at bedtime, 400 mg ORALLY twice daily, or 300 mg ORALLY 4 times daily • Duodenal ulcer disease: active, 800 mg IV at bedtime • Duodenal ulcer disease: maintenance, 400 mg ORALLY at bedtime • Gastric hypersecretion: 300 mg ORALLY 4 times daily with meals and at bedtime up to a maximum of 2400 mg/day • Gastric hypersecretion: 300 mg IV 4 times daily with meals and at bedtime up to a maximum of 2400 mg/day • Gastric ulcer, Active: active, 800 mg ORALLY at bedtime, 400 mg ORALLY twice daily, or 300 mg ORALLY 4 times daily • Gastric ulcer, Active:	• Esophagitis: 20-40 mg ORALLY twice daily • Gastric hypersecretion: 20-160 mg ORALLY every 6 hours OR 20 mg IV every 12 hours • Gastroesophageal reflux disease: 20-40 mg ORALLY twice daily • Gastrointestinal ulcer: active ulcer treatment, 40 mg ORALLY at bedtime OR 20 mg IV every 12 hours • Gastrointestinal ulcer: maintenance therapy, 20 mg ORALLY at bedtime • Hyperchlorhydria: 10-20 mg ORALLY twice daily Details in DRUGDEX® FAMOTIDINE

Topics:	Column One	Column Two
	CIMETIDINE	**FAMOTIDINE**
	active, 800 mg IV at bedtime • Gastric ulcer, Maintenance: maintenance, 400 mg ORALLY at bedtime • Gastroesophageal reflux disease: 1600 mg ORALLY daily in divided doses, 800 mg twice daily or 400 mg 4 times daily for 12 weeks • Gastroesophageal reflux disease: 1600 mg IV daily in divided doses, 800 mg twice daily or 400 mg 4 times daily for 12 weeks • Stress ulcer; Prophylaxis: 50 mg/hour continuous IV infusion for up to 7 days Details in DRUGDEX® CIMETIDINE	
Pediatric Dose	• Duodenal ulcer disease: not recommended in children under 16 yrs; however, if in the judgment of the physician the benefit outweighs the risk, in very limited experience, doses of 20-40 mg/kg/day have been used for the treatment of active duodenal ulcers Details in DRUGDEX® CIMETIDINE	• Gastroesophageal reflux disease: (1-16 yrs) 1 mg/kg/day ORALLY divided twice daily up to 40 mg twice daily • Gastrointestinal ulcer: (1-16 yrs) 0.5 mg/kg/day ORALLY at bedtime or twice daily up to a maximum of 40 mg/day; 0.25 mg/kg IV every 12 hours up to a maximum of 40 mg/day Details in DRUGDEX® FAMOTIDINE
Dose Adjustments	• renal impairment: CrCL less than 30mL/min, half	• renal impairment: (adult) CrCl less than 50 mL/min,

Topics:	Column One	Column Two
	CIMETIDINE	**FAMOTIDINE**
	of the recommended dose • severe renal impairment: caution recommended, 300 mg every 12 hours, may increase to every 8 hours • severe liver disease: 50% reduction in the dose Details in DRUGDEX® CIMETIDINE	50% of dose or increase dosing interval to 36-48 hours • renal impairment: (pediatric) CrCl 30-60 mL/min/1.73 m(2), give 50% of dose • renal impairment: (pediatric) CrCl less than 30 mL/min/1.73 m(2), give 25% of dose Details in DRUGDEX® FAMOTIDINE
Administration	• IV administration: dilute in 50mL of D5W or NS, infuse over 15-20min	• dilute in 5-10 mL NS or D5W and give IV push over 2 mins, OR dilute in 100 mL and infuse over 15-30 min • oral disintegrating tablets: use dry hands to remove the tablet from the blister unit, place the tablet on the tongue allowing it to disintegrate, then swallow with saliva
How Supplied	• Oral Solution: 300 MG/5 ML • Oral Suspension: 200 MG/20 ML • Oral Tablet: 100 MG, 200 MG, 300 MG, 400 MG, 800 MG	• Intravenous Solution: 0.4 MG/ML, 20 MG/50 ML, 10 MG/ML • Oral Powder for Suspension: 40 MG/5 ML • Oral Tablet: 10 MG, 20 MG, 40 MG • Oral Tablet, Chewable: 10 MG • Oral Tablet, Disintegrating: 20 MG, 40 MG

Topics:	Column One	Column Two
	CIMETIDINE	**FAMOTIDINE**
Indications	• **FDA labeled indications** • Duodenal ulcer disease • Gastric hypersecretion • Gastric ulcer, Active • Gastric ulcer, Maintenance • Gastroesophageal reflux disease • Stress ulcer; Prophylaxis Details in DRUGDEX® CIMETIDINE	• **FDA labeled indications** • Esophagitis • Gastroesophageal reflux disease • Gastrointestinal ulcer • Hyperchlorhydria • **Non-FDA labeled indications** • Gastric hypersecretion Details in DRUGDEX® FAMOTIDINE
Contraindications	• hypersensitivity to cimetidine or other H2-antagonist Details in DRUGDEX® CIMETIDINE	• hypersensitivity to famotidine Details in DRUGDEX® FAMOTIDINE
Precautions	• rapid administration by intravenous bolus has caused cardiac arrhythmias and hypotension • renal failure • patients with pseudohypoparathyroidism may be more sensitive to neurotoxic effects of cimetidine • may suppress responses to immediate skin tests • symptomatic response to cimetidine therapy does not preclude the presence of a gastric malignancy • CNS psychosis occurs predominately in severely ill patients • may increase the	• severe renal insufficiency • symptomatic response to famotidine therapy does not preclude the presence of gastric malignancy • may increase the possibility of hyperinfection of strongyloidiasis, especially in immunocompromised patients

Topics:	Column One	Column Two
	CIMETIDINE	**FAMOTIDINE**
	possibility of hyperinfection of strongyloidiasis, especially in immunocompromised patients	
Adverse Effects	• **COMMON** • Dermatologic: Rash • Endocrine metabolic: Gynecomastia • Gastrointestinal: Diarrhea • Neurologic: Dizziness, Headache • **SERIOUS** • Hematologic: Agranulocytosis (rare) • Psychiatric: Psychotic disorder (rare) Details in DRUGDEX® <u>CIMETIDINE</u>	• **COMMON** • Gastrointestinal: Constipation, Diarrhea • Neurologic: Dizziness • **SERIOUS** • Hepatic: Increased liver enzymes (rare) Details in DRUGDEX® <u>FAMOTIDINE</u>
Drug Interaction	• **Contraindicated** • Dofetilide (probable) • **Major** • Carmustine (theoretical) • Chloroquine (probable) • Meperidine (probable) • Metformin (established) • Morphine (probable) • Theophylline (probable) • Tizanidine (theoretical) • Tolazoline (theoretical)	• **Major** • Tolazoline (theoretical) • **Moderate** • Cefditoren Pivoxil (probable) • Cefpodoxime Proxetil (probable) • Cyclosporine (probable) • Itraconazole (established) Details in DRUGDEX® <u>FAMOTIDINE</u>

Topics:	Column One	Column Two
	CIMETIDINE	**FAMOTIDINE**
	• Zalcitabine (probable) • **Moderate** • Alprazolam (probable) • Amitriptyline (probable) • Azelastine (probable) • Carvedilol (probable) • Cefpodoxime Proxetil (probable) • Clozapine (probable) • Cyclosporine (probable) • Desipramine (probable) • Dilevalol (probable) • Diltiazem (probable) • Doxepin (probable) • Dutasteride (probable) • Epirubicin (probable) • Escitalopram (probable) • Flecainide (probable) • Fluconazole (probable) • Fosphenytoin (probable) • Glipizide (probable) • Imipramine (probable) • Labetalol (probable) • Levomethadyl (probable) • Lidocaine (probable) • Lornoxicam (probable) • Metoprolol (probable) • Midazolam (probable) • Nifedipine (probable) • Nisoldipine (probable) • Nortriptyline (probable) • Paroxetine (probable) • Pentoxifylline (probable) • Phenindione (probable) • Phenytoin (probable) • Pramipexole (probable) • Procainamide (probable) • Propranolol (probable) • Quinidine (probable)	

Topics:	Column One	Column Two
	CIMETIDINE	**FAMOTIDINE**
	• Saquinavir (probable) • Sertraline (probable) • Tacrolimus (probable) • Tamsulosin (probable) • Timolol (probable) • Tocainide (probable) • Trimetrexate (probable) • Warfarin (probable) • Zaleplon (probable) • Zolmitriptan (probable) Details in DRUGDEX® CIMETIDINE	
Pregnancy Category	• B Details in DRUGDEX® CIMETIDINE	• B Details in DRUGDEX® FAMOTIDINE
Breast Feeding	• Infant risk cannot be ruled out. Details in DRUGDEX® CIMETIDINE	• Infant risk cannot be ruled out. Details in DRUGDEX® FAMOTIDINE
Notes		• the oral formulations are bioequivalent

Postgraduate Medical Journal (July 1982) **58**, 415–418

EYh H

Neurological and psychiatric side effects of cimetidine—report of 3 cases with review of the literature

M. SONNENBLICK
M.D.

A. J. ROSIN
M.B., F.R.C.P.

N. WEISSBERG
M.D.

Department of Geriatric Medicine, Shaare Zedek Medical Center, Jerusalem, Israel

Summary

Neurological and psychiatric side effects of cimetidine are reviewed in 47 cases from the literature, and 3 further cases are described. Confusion, psychomotor restlessness, hallucinations and disorientation, stupor and coma were the main features; some had convulsions and a few exhibited focal neurological deficits or neuropathies. The signs appeared within 2 days in almost half of the patients, and remitted in most within 2–3 days. Predisposing factors, of which more than one may be present, are advanced age, hepatic or renal dysfunction, or severe underlying disease. The 3 cases described were all old, one had cirrhosis with bleeding oesophageal varices, and one had renal failure with nephrotic syndrome and amyloidosis.

In view of the increasingly wide use of cimetidine, conditions in which there is decreased metabolic breakdown, or excretion, or predisposition to increased brain levels should prompt careful follow-up, and possibly a lower dosage regimen, especially in elderly patients.

Introduction

1000–1200 mg/d

Cimetidine, the histamine H_2 receptor blocking agent, is widely used for the treatment of duodenal ulcer, and is also administered in peptic oesophagitis, hypersecretory disorders and in acute gastrointestinal bleeding. The drug is generally well tolerated in doses of 1000–1200 mg daily. However, many side effects have been described. The first case of cimetidine-induced mental confusion was reported by Grimson in 1977, but since then mental confusion, psychiatric disorders and neurological abnormalities have been occasionally reported. Predisposing factors for these side effects are claimed to be old age and renal and hepatic failure. Coma in an old person suffering from metabolic failure, and who is receiving cimetidine may thus pose a difficult diagnostic problem. Withdrawal of cimetidine can indicate the probable cause of the clinical deterioration. In this paper 3 elderly patients are described who presented with coma or confusion following the administration of cimetidine. In 2 of them, there was concurrent renal or hepatic failure but the mental state returned to normal on cessation of the drug. Forty-seven patients with neurological and psychiatric disorders due to cimetidine who were reported in the literature from 1977 are reviewed and analysed regarding associations of age and clinical status.

→ see list of [illegible] related" diseases
D. Rosin proposes to Rx.

Case reports

Case 1

1000 mg/d

An 80-year-old woman underwent nail-plate insertion for hip fracture. In the postoperative period she developed pulmonary emboli, and was treated with heparin. At this time renal and liver function tests were in the normal range. Three days later the patient developed monilia oesophagitis. Cimetidine tablets 200 mg 5 times daily were started. One day later the patient became drowsy and confused. No additional pathology was found. Cimetidine was discontinued and 24 hr later she became fully orientated.

Case 2

1000 mg/d

An 82-year-old woman was admitted with haematemesis and melaena. Apart from mild oedema of the legs physical examination was normal, but the haemoglobin was 9·3 g/dl, blood urea nitrogen (BUN) 27 mmol/litre and serum creatinine 415 µmol/litre. Serum albumin was 23 g/litre, but other tests of liver function and serum electrolytes were normal. Endoscopy and biopsy showed acute and chronic oesophagitis and upper gastro-intestinal X-

rays were normal. Cimetidine 1g daily i.v. (200 mg three times daily and 400 mg at night) was given, but this and other conservative measures failed to stop the bleeding, and on the 3rd day laparotomy was performed. The findings at operation were cirrhosis and oesophageal varices and a feeding gastrostomy was performed. Postoperatively she continued to have cimetidine 1 g daily as well as metoclopramide 10 mg 3 times daily. Pitressin was given for 48 hr. On the 7th postoperative day, she became stuporose, and within hours sank into hyporeflexic coma, reacting only to painful stimuli. There was no asterixis. All drugs were stopped, and the patient received i.v. glucose 20%, neomycin 4 g by mouth and 200 mg spironolactone for 24 hr. Within 24 hr the patient became responsive to commands, and 3 days later she was wide awake eating orally. Electroencephalogram (EEG) performed while she was comatose showed slow wave patterns with bursts of fast wave activity, consistent with drug-induced toxic encephalopathy. There were no triphasic waves. A repeat EEG after her return to conciousness showed that the fast wave periodic pattern had disappeared.

Comment. The onset of coma within a few hours, the lack of tremor, the preservation of normal liver function tests, and rapid recovery after stopping cimetidine favour the latter as the cause of her coma rather than hepatic encephalopathy. It is likely that her underlying liver disease predisposed to cimetidine toxicity.

Case 3 800 mg/d

An 80-year-old man with a paraparesis of spinal origin was admitted to hospital with haematemesis, shown by endoscopy to be due to oesophagitis. He had developed moderate anasarca within the previous 6 weeks. The diagnosis of nephrotic syndrome was made by the findings of urine protein of 4 g daily and serum albumin of 16–24 g/litre, and BUN of 32 mmol/litre. Rectal biopsy, bone marrow and subsequent liver biopsy showed widespread amyloidosis. Cimetidine 200 mg 4 times daily was given i.v. and thereafter by mouth. On the 8th day, the patient became comatose, reacting only to pain but with no jaundice or asterixis. There was no change in pre-existing renal function tests, and the liver enzyme levels. EEG showed periodic fast low amplitude complexes, compatible with drug-induced effects. Cimetidine was discontinued and mental recovery ensued, although frontal lobe release signs and psychomotor restlessness continued for 24 hr after stopping the drug. The patient was conscious with mild disorientation by the second day after withdrawal of cimetidine, and fully alert by the 4th day.

Comment. The onset of coma without deterioration in the biochemical profile was suggestive of a cause other than the renal failure. Recovery of consciousness within 2 days of stopping cimetidine pointed to this as the precipitating cause; even in modified dosage of cimetidine the presence of renal failure potentiated the drug's effects on the central nervous system.

Review of literature

Survey of the literature from 1977 to 1981 revealed 47 other patients who were reported as suffering from neuropsychiatric disorders induced by cimetidine (Adler, Sadja and Wilets, 1980; Aelaney and Ravey, 1977; Agarwal 1978; Arneson, 1979; Atkinson, 1980; Bacigalupo, Van-Lint and Marmont, 1978; Bale, 1979; Barbier and Hirsch, 1978; Barnhart and Bowden, 1979; Basavaraju *et al.* 1980; Cumming and Forster, 1978; Delaunois, 1979; Edmonds, Ashford and Brenner, 1979; Grimson 1977; Jefferson, 1979; Johnson and Bailey, 1979; Kimelblatt, 1980; Kinell and Webb, 1979; Klotz and Key, 1978; Levine, 1978, McMillen, Ambis and Siegel, 1978; Menzies-Gow, 1977; Mogelnicki, Waller and Finlayson, 1979; Nelson, 1977; Petite and Bloch, 1978; Quap, 1978; Robinson and Mulligan, 1977; Schentag *et al.*, 1979; Vickery, 1978; Walls, Pearce and Venables, 1980; Weddington *et al.*, 1981; Wood, Isaacson and Hibbs, 1978). up to 1200 mg/d

Twenty-seven of the patients were male and 19 female, in 4 patients the sex was not reported. The age of 19 patients was 65 years and above, and 27 patients were under the age of 65 years. Conventional doses (up to 1200 mg/24 hr or 20 mg/kg/24 hr) were administered in 45 patients; 5 patients took excess doses. The route of administration was by mouth in 21 and intravenously in 21 patients. Table 1 summarizes the time interval from the onset of treatment until the appearance of the neuropsychiatric side effects. In those cases in which the side effects appeared after increasing the dose of cimetidine the time at which side effects appeared was stated as from the day on which the dose was increased. In 50% neurotoxic effects were prominent within 48 hr. The time until remission occurred was the interval from the day on which the dose was reduced or stopped until relief of symptoms occurred. Almost two-thirds had returned to normal within 2 days. In 5 patients reduction of the dose without stopping the cimetidine brought about relief of the side effects.

The main clinical manifestations were mental confusion (52%), stupor or coma (22%) and neurological abnormalities (16%) such as peripheral neuropathy and pyramidal signs. Psychiatric complications were found in 10% and included depression and paranoid states. Not good for Schizophrenia

The possible risk factors for developing cimetidine-induced toxicity are analysed in Table 2. Severe

very of conscious-
netidine pointed to
even in modified
ce of renal failure
he central nervous

77 to 1981 revealed
d as suffering from
ced by cimetidine
elaney and Ravey,
79; Atkinson, 1980;
mont, 1978; Bale,
Barnhart and Bow-
80; Cumming and
Edmonds, Ashford
7; Jefferson, 1979;
iblatt, 1980; Kinell
1978; Levine, 1978;
978; Menzies-Gow,
tlayson, 1979; Nel-
1978; Quap, 1978;
chentag *et al.*, 1979;
nd Venables, 1980;
saacson and Hibbs,

were male and 19
not reported. The
and above, and 27
years. Conventional
mg/kg/24 hr) were
atients took excess
n was by mouth in
ts. Table 1 summa-
onset of treatment
uropsychiatric side
ch the side effects
se of cimetidine the
ared was stated as
e was increased. In
ninent within 48 hr.
ed was the interval
se was reduced or
s occurred. Almost
d within 2 days. In 5
ithout stopping the
f the side effects.
tions were mental
(22%) and neurolo-
s peripheral neuro-
iatric complications
led depression and

developing cimeti-
d in Table 2. Severe

TABLE 1. Number of patients in relation to the time of appearance of signs of cimetidine neurotoxicity after the beginning of treatment and the remission of toxic signs after reducing or stopping the drug

	Appearance of signs	Disappearance of signs
0–2 days	24	32
3–7 days	8	8
>7 days	10	2
Not reported	8	8

systemic illness without primary disease of the liver or kidney was found in 4 patients. In 6 other patients a gross systemic disease was present in addition to either renal or hepatic failure or both.

TABLE 2. Predisposing factors to cimetidine neurotoxicity

	No. of patients	%
Impaired renal function	10	20
Impaired renal and hepatic function	6	12
Impaired hepatic function	1	2
Severe underlying disease	4	8
High dose of cimetidine	4	8

Discussion

The literature review indicated that of 50 patients showing neurotoxicity from cimetidine, about 40% were aged 65 years or over. This proportion of elderly patients is much higher than expected among all patients taking cimetidine. Extensive toxicological and pharmacological studies in animals have failed to detect cimetidine in the central nervous system, and neurotoxicity has not been noted (Brimblecombe & Duncan, 1977; Burland et al., 1979; Canavan & Briggs, 1977). Studies in man, however, have shown that the drug may cross the blood brain barrier. Schentag *et al.*, (1979) found in 5 patients with severe mental confusion following cimetidine administration that measurable amounts were detectable in the cerebrospinal fluid (CSF). Levels higher than 0·8 mg/ml were considered toxic. In one other report of 2 patients with neurotoxicity, CSF cimetidine levels of 0·82 mg/ml and 0·76 mg/ml were found (Edmonds *et al.*, 1979). These findings suggest that the neurotoxic effect may occur because cimetidine is blocking histamine H_2 receptors in the brain.

There are a few factors which may contribute to the elevation of the CSF levels of cimetidine. High serum concentration is a possibility, which in 5 patients may have been due to treatment with over dosage of cimetidine. However, excessive dosage was without side effects in a few patients (Gill, 1978; Illingworth & Jarvie, 1979). Other causes for high serum cimetidine concentration are impaired clearance of the drug. Seventeen patients (34%) suffered from impaired hepatic function, renal function or both. The plasma half-life of cimetidine in patients with severe renal failure is doubled (Luk, Luk and Hendrix, 1979). Furthermore cimetidine itself reduces creatinine clearance, and thereby might potentiate its own effect by an increased serum half-life. In addition to this, patients with liver disease showed a CSF/serum cimetidine ratio higher than normal (>0·24) (Schentag *et al.*, 1979), and this suggests the possibility of higher penetrability of the central nervous system to cimetidine.

Nearly 60% of the patients showed signs of toxicity within 2 days of the onset of treatment. Furthermore a few of the patients did not have renal or hepatic failure, or significant underlying disease, and were treated with conventional doses. Such cases indicate a possible individual susceptibility to the effects of cimetidine on the brain. However, elderly patients, including those reported in this paper may present several simultaneous causes for lapse into coma and it is important to appreciate that the presence of renal or hepatic insufficiency may itself potentiate the cerebral effects of cimetidine. Where neurotoxicity is related to one of the above risk factors mentioned, dosage should be decreased and one might expect reversal of mental impairment, as was the case in five patients.

In patients with renal failure, the dosage regimen has been recommended as follows: serum creatinine over 354 μmol/l —150 mg 4 times daily; 177–354 μmol/l—225 mg 4 times daily; less than 177 μmol/l—300 mg 4 times daily (Luk *et al.*, 1979).

This review of 50 patients suggests that cimetidine may be neurotoxic, particularly in old age, in debilitated patients, and in patients with renal or hepatic failure. In all these conditions, patients may be more sensitive to mental changes. However, as cessation of cimetidine resulted in remission in all of the patients and in most of them within 48 hr, use of the drug is not contraindicated in these patients. It is, however, recommended to start treatment with reduced dosage, and to monitor neurological and mental status.

Although trials of a new antihistamine H_2 receptor blocker ranitidine revealed few side effects (Walt *et al.*, 1981), avoidance of neurotoxicity in the presence of renal failure still demands a smaller total daily dose of ranitidine (Bories *et al.*, 1980; Sharpe and Burland, 1980).

References

ADLER, L.E., SADJA, L. & WILETS, G. (1980) Cimetidine toxicity

without renal failure
CIME recommended @
300 mg 4x/day
Note: Patients w/ renal failure cannot take CQ.

manifested as paranoia and hallucinations. *American Journal of Psychiatry*, **137**, 1112.

Adlaney, J. & Ravey, M. (1977) Cimetidine and mental confusion (letter). *Lancet*, **ii**, 512.

Agarwal, S.K. (1978) Cimetidine and visual hallucinations (letter). *Journal of American Medical Association*, **240**, 214.

Arneson, G.A. (1979) More on toxic psychosis with cimetidine (letter). *American Journal of Psychiatry*, **136**, 1349.

Atkinson, A.B. (1980) Neurological dysfunction in two patients receiving captopril and cimetidine (letter). *Lancet*, **ii**, 36.

Baccigalupo, A., Van-Lint, M.T. & Marmont, A.M. (1978) Cimetidine induced coma (letter). *Lancet*, **ii**, 45.

Bale, J.F. (1979) Cimetidine induced cerebral toxicity in children (letter). *Lancet*, **i**, 725.

Barbier, J.P.H. & Hirsch, J.F. (1978) Confusion mentale chez un malade traite par la cimetidine. *Nouvelles Presses Medicales*, **7**, 1484.

Bories, P., Michel, H., Duclos, B. & Mirouze, J. (1980) Use of ranitidine without mental confusion in patient with renal failure. *Lancet*, **ii**, 755.

Burland, W.L., Gleadle, R.I., Lee, R.M., Rowley-Jones, D. & Groom, G.V. (1979) Prolactin responses to cimetidine. *British Journal of Clinical Pharmacology*, **7**, 19.

Barnhart, C.C. & Bowden, C.L. (1979) Toxic psychosis with cimetidine. *American Journal of Psychiatry*, **136**, 725.

Basavaraju, N.G., Wolf-Klein, G., Silverstone, F.A. & Libow, L.S. (1980) Cimetidine induced mental confusion in elderly. *New York State Journal of Medicine*, **80**, 1287.

Brimblecombe, R.W. & Duncan, W.A.M. (1977) *Proceedings of the second internation symposium on histamine H. receptor antagonists*. p. 54. (Ed. Burland, W.L. & Simkins, M.A.). Excerpta Medica, Amsterdam.

Canavan, J.S.F. & Briggs, J.D. (1977) *Proceedings of the second international symposium on histamine H. receptor antagonists*. P. 75. (Ed. by Burland, W.L. & Simkins, M.A.). Excerpta Medica, Amsterdam.

Cumming, W.J.K. & Forster, J.B. (1978) *Cimetidine induced brainstem dysfunction* (letter). *Lancet*, **i**, 1096.

Delaunois, L. (1979) Hypersensitivity to cimetidine (letter). *New England Journal of Medicine*, **300**, 1216.

Edmonds, M.E., Ashford, F.F.U. & Brenner, M.K. (1979) Cimetidine: does neurotoxicity occur? *Journal of the Royal Society of Medicine*, **72**, 172.

Gill, G.V. (1978) Cimetidine overdose. *Lancet*, **i**, 99.

Grimson, T.A. (1977) Reaction to cimetidine (letter). *Lancet*, **i**, 858.

Illingworth, R.N. & Jarvie, D.R. (1979) Absence of toxicity in cimetidine overdosage. *British Medical Journal*, **1**, 453.

Jefferson, J.W. (1979) Central nervous system toxicity of cimetidine. A case of depression. *American Journal of Psychiatry*, **136**, 346.

Johnson, J. & Bailey, S. (1979) Cimetidine and psychiatric complication. *British Journal of Psychiatry*, **134**, 315.

Kimelblatt, B.J. (1980) Dose and serum concentration relationships in cimetidine associated mental confusion. *Gastroenterology*, **78**, 791.

Kinell, H.G. & Webb, A. (1979) Confusion with cimetidine—the most troublesome adverse effect (letter). *British Medical Journal*, **2**, 1438.

Klotz, S.A. & Key, B.F. (1978) Cimetidine and agranulocytosis. *Annals of Internal Medicine*, **88**, 579.

Levine, M.L. (1978) Cimetidine induced coma in cirrhosis of the liver. *Journal of the American Medical Association*, **240**, 1238.

Luk, C.D. & Luk, W.J. & Hendrix, T.R. (1979) Cimetidine and impaired renal function. *Annals of Internal Medicine*, **90**, 991.

McMillen, M.A., Ambis, D. & Siegel, J.H. (1978) Cimetidine and mental confusion (letter). *New England Journal of Medicine*, **298**, 284.

Menzies-Gow, N. (1977) Cimetidine and mental confusion (letter). *Lancet*, **ii**, 928.

Mogelnicki, S.R., Waller, J.L. & Finlayson, D.C. (1979) Physostigmine reversal of cimetidine induced mental confusion. *Journal of the American Medical Association*, **241**, 826.

Nelson, P.G. (1977) Cimetidine and mental confusion (letter). *Lancet*, **ii**, 928.

Petite, J.P. & Bloch, F. (1978) Syndrome depress au cours d'un traitment par la cimetidine (letter). *Nouvelles Presses Medicals*, **8**, 1260.

Quap, C.W. (1978) Confusion: An adverse reaction to cimetidine therapy (letter). *Drug Intelligence and Clinical Pharmacy*, **12**, 121.

Robinson, T.J. & Mulligan, T.O. (1977) Cimetidine and mental confusion (letter). *Lancet*, **ii**, 719.

Sawyer, D., Conner, C.S. & Scalley, R. (1981) Cimetidine: Adverse reaction and acute toxicity. *American Journal of Hospital Pharmacy*, **38**, 188.

Schentag, J.J., Cerra, F.B., Calleri, G., DeGlopper, E., Rose, J.Q. & Bernhard, H. (1979) Pharmacokinetic and clinical studies in patients with cimetidine associated mental confusion. *Lancet*, **ii**, 177.

Sharpe, P.C. & Burland, W.L. (1980) Mental confusion and H. receptor blockers. *Lancet*, **ii**, 924.

Vickers, T.R. (1978) Cimetidine reaction. *Drug Intelligence and Clinical Pharmacy*, **12**, 242.

Walls, T.J., Pearce, S.J. & Venables, G.S. (1980) Motor neuropathy associated with cimetidine. *British Medical Journal*, **281**, 974.

Walt, R.P., Trotman, I.F., Frost, R., Golding, P.L., Shepherd, T.H., Rawlings, J., Hunt, R.H., Colin-Jones, D., Milton-Thompson, G.J. & Misiewicz, J.J. (1981) Comparison of twice-daily ranitidine with standard cimetidine treatment of duodenal ulcer. *Gut*, **22**, 319.

Weddington, W.W., Muelling, A.E., Moosa, H.H., Kimball, C.P. & Rowlett, R.P. (1981) Cimetidine toxic reaction masquerding as delirium tremens. *Journal of the American Medical Association*, **245**, 1058.

Wood, C.A., Isaacson, M.L. & Hibbs, M.S. (1978) Cimetidine and mental confusion (letter). *Journal of the American Medical Association*, **239**, 2550.

Exh I

Cimetidine: does neurotoxicity occur? Report of three cases[1]

M E Edmonds BSc MRCP
R F U Ashford MA MRCP
M K Brenner MA MRCP
A Saunders MD MRCP
Departments of Therapeutics and Rheumatology, Westminster Hospital, London SW1P 2AP, and St Stephen's Hospital, London SW10 9TH

There have been several reports of neurotoxicity attributed to cimetidine. These include confusion (Grimson 1977, Delaney & Raven 1977, McMillen *et al.* 1978, Wood *et al.* 1978) and twitching (Grave *et al.* 1977). In none have plasma cimetidine estimations been performed. Here we report three cases of neurotoxicity in which the plasma cimetidine concentration was estimated. Cimetidine was present in the CSF of two of the cases. The causative role of cimetidine is discussed.

Case 1

A 58-year-old woman with a past history of diverticulitis presented with lower abdominal pain. After a period of conservative management with antibiotics laparotomy was performed. A perforated pericolic abscess, generalized peritonitis, and subphrenic abscesses were found. The abscesses were drained and a transverse colostomy performed. Postoperative complications were pulmonary oedema, wound infection with faecal fistula formation and recurrent subphrenic abscess. Infection was treated with benzylpenicillin, metronidazole and gentamicin. Following exploration of the left subphrenic space she again developed pulmonary oedema and required temporary ventilation. She developed oliguria which, despite discontinuing gentamicin, progressed to anuria. Cimetidine syrup 100 mg six hourly was started following aspiration of blood via the nasogastric tube. She was haemodialysed for three weeks during which time she received cimetidine 200 mg eight hourly i.v. She was drowsy throughout. When spontaneous diuresis commenced, haemodialysis was stopped. Three days later she became confused and following a right Jacksonian fit, developed status epilepticus. This was uncontrolled by diazepam 20 mg i.v., phenytoin 500 mg i.m., 10 ml 10% calcium gluconate and 2 ml 50% magnesium sulphate. Thiopentone 350 mg i.v. hourly was necessary to achieve control. At this time plasma sodium was 139, potassium 3.3, urea 20.0, glucose 6.3 mmol/l. CSF showed RBC 0, WBC 0, protein 0.12 g/l. CAT scan was normal. Plasma cimetidine concentration was 7.5 mg/l, and CSF cimetidine concentration 0.82 mg/l (high pressure liquid chromatography method) (Randolph *et al.* 1977). She was also receiving benzylpenicillin 1.5 megaunits eight hourly i.v., gentamicin 60 mg i.v. daily (with plasma level monitoring) and metronidazole 2 g eight hourly *per rectum* for persistent sepsis. Metronidazole levels were low at 28.8 µg/ml (polarographic method) (Kane 1961). Cimetidine was reduced to 200 mg i.v. daily. Penicillin, gentamicin and metronidazole were stopped. She recovered consciousness and had no further fits. Subsequently renal function recovered but reexploration of the abdomen 2 months later revealed an adenocarcinoma of the left ovary and the patient subsequently died.

600 mg IV = AEs

300 mg/d IV NO AEs

Normal CIME [CSF: serum] [1 : 4]

Case 2

A 72-year-old man with osteoarthritis, gout, psoriasis, hypertension and mild chronic renal failure, sustained a gastrointestinal bleed whilst an inpatient. He was on azapropazone 300 mg six hourly. Prior to this c… creatinine 250 µmol/l. H… The next day he becam… cimetidine concentration… 39.3 mmol/l and creatini… on the third day of cimet… He continued to bleed, … catheterization. After thi… of the twitching had furt… 1.57 mg/l. Urea was 51.… that day he underwent ga… Postoperatively cimetidir… twitching was again evid… dose) was 2.92 mg/l and… reduced to 100 mg six… concentration (2 h 30 m… 320 µmol/l. No twitching… had a further melaena an… day the patient became… cimetidine concentratior… creatinine 225 µmol/l. He… fourteenth day the patien… cimetidine concentration… urea had fallen to 11.3 m… confused or twitching. Th… the clinical course of this…

Case 3

A 62-year-old man was ad… with benzylpenicillin. Hy…

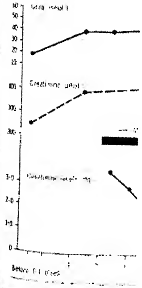

Figure 1 Cimetidine neurotoxici… cimetidine concentration during…

[1] Accepted 3 October 1978

0141-0768/79/030172-04/$01.00/0

3.53 mg

six hourly. Prior to this event his creatinine clearance was 13 ml/minute, urea 18.3 mmol/l, and creatinine 250 µmol/l. He was transfused and started on cimetidine 200 mg eight hourly i.v. The next day he became confused and widespread muscular twitching was noted. Plasma cimetidine concentration was 3.53 mg/l (4 hours after his first dose of cimetidine). His urea was 19.3 mmol/l and creatinine 290 µmol/l. Cimetidine was reduced to 200 mg twice daily i.v. and on the third day of cimetidine therapy twitching was less noticeable and he was less confused. He continued to bleed, was further transfused and required urethral dilatation prior to catheterization. After this he had a good diuresis. On the fourth day the frequency and extent of the twitching had further lessened. Plasma cimetidine concentration (90 min after dose) was 1.57 mg/l. Urea was 51.0 mmol/l and creatinine 420 µmol/l. Following a further bleed later that day he underwent gastroduodenotomy, vagotomy and oversewing of three pyloric ulcers. Postoperatively cimetidine was increased to 200 mg six hourly and on the next (fifth) day the twitching was again evident. At this time the plasma cimetidine concentration (90 min after dose) was 2.92 mg/l and urea had fallen to 26.0 mmol/l. On the sixth day cimetidine was reduced to 100 mg six hourly and the twitching was less evident. Plasma cimetidine concentration (2 h 30 min after dose) was 0.95 mg/l, urea 32.6 mmol/l and creatinine 320 µmol/l. No twitching was observed on the seventh day but at 18:00 that day the patient had a further melaena and cimetidine was increased to 200 mg eight hourly i.v. On the eighth day the patient became more confused but no further twitching was observed. Plasma cimetidine concentration (2 h 30 min after dose) was 1.04 mg/l, urea 20.0 mmol/l and creatinine 225 µmol/l. He was transfused again but after this had no further bleeds. On the fourteenth day the patient was changed to cimetidine 200 mg eight hourly orally. The plasma cimetidine concentration (90 min after dose) was 2.36 mg/l on the sixteenth day. By then the urea had fallen to 11.3 mmol/l and creatinine was 120 µmol/l, and the patient was no longer confused or twitching. The blood urea, creatinine and plasma cimetidine concentration during the clinical course of this patient are charted below (Figure 1). The patient has now recovered.

600 mg/d IV : n
400 mg IV ? n
CIME 800 mg/d = AEs 272 mg/l plasma levels
plasma CIME 1.57 mg
CIm 1/2 life i.v. = 1.5-2 h

→ 600 mg/d orally, no AEs

Case 3

Still lower than Di Rocco's suggested dose.

A 62-year-old man was admitted to hospital with pneumococcal pneumonia which was treated with benzylpenicillin. Hypocalcaemia and tetany of unknown aetiology developed 24 hours

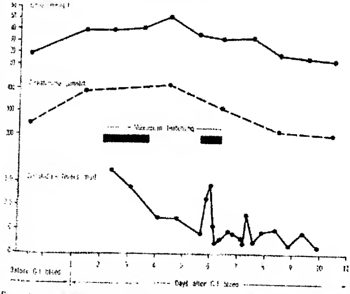

Figure 1. Cimetidine neurotoxicity in renal failure. Blood urea, creatinine and plasma cimetidine concentration during clinical course of Case 2

... cimetidine. These include ... 1978, Wood *et al.* 1978) and ... stimations been performed. ... metidine concentration was ... ases. The causative role of

... with lower abdominal pain. ... trotomy was performed. A ... abscesses were found. The ... ostoperative complications ... formation and recurrent ... ronidazole and gentamicin. ... eloped pulmonary oedema ... nich, despite discontinuing ... ourly was started following ... sed for three weeks during ... drowsy throughout. When ... hree days later she became ... itus epilepticus. This was ... 10% calcium gluconate and ... was necessary to achieve ... a 20.0, glucose 6.3 mmol/l ... normal. Plasma cimetidine ... 2 mg/l (high pressure liquid ... ceiving benzylpenicillin 1.5 ... sma level monitoring) and ... tronidazole levels were low ... was reduced to 200 mg i.v. ... e recovered consciousness ... but reexploration of the ... eft ovary and the patient

... on and mild chronic renal ... is on azapropazone 300 mg

after admission. This responded to 80 ml of 10% calcium gluconate, after which the plasma calcium concentration was 2.38 mmol/l. Two days after admission a diagnosis of pneumococcal meningitis was confirmed by lumbar puncture and he was given a single dose of 10 000 units of intrathecal penicillin. Acute renal failure developed concurrently and was treated with peritoneal dialysis.

800 mg/d

Two days later, following a haematemesis, he was started on cimetidine 200 mg twice daily i.v. which was subsequently increased to 200 mg six hourly i.v. Twenty-four hours later (after 4 doses) he developed grand mal convulsions uncontrollable by conventional anticonvulsants. Control was obtained by curarization and intravenous infusion of thiopentone. Repeat lumbar puncture was unchanged. Plasma sodium, potassium, calcium and magnesium were all normal. Urea was 35.0 mmol/l. The plasma cimetidine concentration was 1.75 mg/l. CSF cimetidine concentration was 0.76 mg/l. Cimetidine was discontinued and after 24 hours no further convulsions occurred, although he did not fully regain consciousness. He subsequently developed pseudomonas septicaemia and died. Permission for autopsy was refused.

Discussion

Although the neurotoxicity described in these cases is multifactorial we believe cimetidine played an important role in Cases 1 and 2. In Case 1 in spite of renal impairment and sepsis we found no metabolic or infective cause for the convulsions. The dose of penicillin was not excessive. Metronidazole levels were low and we know of no reports of this agent causing convulsions. Plasma cimetidine concentration was high at 7.5 mg/l. (Normal range 2 hours after dose: 0.5–3.0 mg/l). CSF cimetidine was 0.82 mg/l. Cimetidine accumulation occurred when haemodialysis was discontinued, as the usual route of elimination via the urine was not available. The drug is cleared well by haemodialysis (Canavan *et al.* 1977). In Case 2, the occurrence of twitching correlated with the plasma cimetidine concentration only whilst the patient was uraemic. There was no correlation between the plasma cimetidine concentration and mental confusion in this patient (*see* Figure 1). In Case 3 convulsions occurred only whilst the patient was on cimetidine; however, there is a 25 per cent incidence of convulsions in pneumococcal meningitis (Dodge & Swartz 1965), making a relationship to drug therapy appear less likely. In addition this patient was receiving penicillin. It is of interest to note that cimetidine was detected in the CSF, and that the CSF/plasma cimetidine ratio was 0.43, as compared to 0.11 in Case 1. This may not be surprising in view of the effect of meningitis on the permeability characteristics of the blood-brain barrier.

Increased permeability of the blood-brain barrier has also been reported in renal failure (Fishman & Raskin 1965, Smithers *et al.* 1975). This could explain why in Case 2 the comparatively high cimetidine level on the sixteenth day was not associated with twitching, as by this time the patient was not uraemic, and therefore less cimetidine would have crossed the blood-brain barrier.

Previous reports have linked cimetidine neurotoxicity and renal failure (McMillen *et al.* 1978, Wood *et al.* 1978). Grave *et al.* (1977) noted twitching in a man of 81 given cimetidine 200 mg six hourly i.v. for erosive gastritis following prostatectomy. At the time he was in renal failure with a blood urea of 21 mmol/l. It is of interest that no cases of neurotoxicity were reported in a large series of patients given cimetidine following renal transplantation (Jones *et al.* 1978).

There are no previous reports in the literature of cimetidine crossing the blood-brain barrier in man. Extensive toxicological and pharmacological studies in animals have failed to detect cimetidine in the central nervous system and neurotoxicity has not been noted (Brimblecombe & Duncan 1977, Leslie & Walker 1977, Cross 1977). The fact that hyperprolactinaemia can be induced by cimetidine (Delle Fave *et al.* 1977), suggests that the drug may cross the blood-brain barrier in certain circumstances. The precise mechanism for this effect remains unclear (Burland *et al.* 1979).

The cases presented in this report suggest that cimetidine may be neurotoxic in debilitated patients especially when the blood-brain barrier is compromised. Until there have been further studies correlating clinical signs with levels of cimetidine in blood and CSF, cimetidine should

be used with cautior
cimetidine daily dosa

Summary

Three cases of encep
patients had impair
Measurable amounts
drug can cross the b
impairment is signific

Acknowledgments: W
for permission to repo
on plasma and CSF: D
for their helpful comn
estimations.

References

Brimblecombe R W & Dunc
Receptor Antagonists. Ed
Burland W L, Gleadle R I,
7, 19
Canavan J S F & Briggs J D
Antagonists. Ed. W L Bur
Cross S A M (1977) *Proceed*
Delaney J C & Raven M (19
Delle Fave G F, Tamburrano
Dodge P R & Swartz M N (1
Fishman R A & Raskin N H
Grave W, Nadorp J H S M &
Grimson T A (1977) *Lancet* i,
Jones R H, Rudge C J, Bewic
Kane P O (1961) *Journal of*
Leslie G B & Walker T F (1
Antagonists. Ed. W L Burl
McMillen M A, Ambis D & S
Randolph W C, Osborne V L,
Smithers J L, Nichols P J & M
Wood C A, Isaacson M L & I

mate, after which the plasma
in a diagnosis of pneumococ-
in a single dose of 10 000 units
rently and was treated with

cimetidine 200 mg twice daily
venty-four hours later (after 4
onventional anticonvulsants,
f thiopentone. Repeat lumbar
m and magnesium were all
ntration was 1.75 mg/l. CSF
inued and after 24 hours no
nsciousness. He subsequently
utopsy was refused.

torial we believe cimetidine
nal impairment and sepsis we
e dose of penicillin was not
reports of this agent causing
ng/l. (Normal range 2 hours
idine accumulation occurred
ination via the urine was not
et al. 1977). In Case 2, the
oncentration only whilst the
ma cimetidine concentration
vulsions occurred only whilst
incidence of convulsions in
relationship to drug therapy
t. It is of interest to note that
cimetidine ratio was 0.43, as
the effect of meningitis on the

een reported in renal failure
explain why in Case 2 the
associated with twitching, as
idine would have crossed the

nal failure (McMillen et al.
a man of 81 given cimetidine
y. At the time he was in renal
cases of neurotoxicity were
nal transplantation (Jones et

ssing the blood-brain barrier
animals have failed to detect
it been noted (Brimblecombe
hyperprolactinaemia can be
ug may cross the blood-brain
this effect remains unclear

be neurotoxic in debilitated
Until there have been further
l and CSF, cimetidine should

be used with caution in renal impairment. Where renal impairment is significant the total cimetidine daily dosage should not exceed 400 mg, as is suggested in the official data sheet.

Summary

Three cases of encephalopathy associated with cimetidine therapy are presented. All three patients had impaired renal function and had received cimetidine in standard dosage. Measurable amounts of cimetidine were present in the CSF of two patients, confirming that the drug can cross the blood-brain barrier in man under certain circumstances. Where renal impairment is significant, the total daily dosage of the drug should be appropriately reduced.

Acknowledgments: We thank Professor A F Lant, Dr R D Sturrock and Dr L W Loughridge for permission to report these cases; Dr R M Lee, who performed the cimetidine estimations on plasma and CSF; Dr A C Flind and Dr B Dickson of Smith Kline and French Laboratories for their helpful comments; and Mr D Jackson of May and Baker Ltd for the metronidazole estimations.

References

Brimblecombe R W & Duncan W A M (1977) Proceedings of the Second International Symposium on Histamine H_2-Receptor Antagonists. Ed. W L Burland & M A Simkins. Excerpta Medica, Amsterdam; p 54
Burland W L, Gleadle R I, Lee R M, Rowley-Jones D & Groom G V (1979) *British Journal of Clinical Pharmacology* 7, 19
Canavan J S F & Briggs J D (1977) Proceedings of the Second International Symposium on Histamine H_2-Receptor Antagonists. Ed. W L Burland & M A Simkins. Excerpta Medica, Amsterdam; p 75
Cross S A M (1977) *Proceedings of the European Society of Toxicology* **18**, 288
Delaney J C & Raven M (1977) *Lancet* ii, 512
Delle Fave G F, Tamburrano G, De Magristris L, Natoli C, Santaro M L, Carratu R & Torsoli A (1977) *Lancet* i, 1319
Dodge P R & Swartz M N (1965) *New England Journal of Medicine* **272**, 954
Fishman R A & Raskin N H (1965) *Transactions of the American Neurological Association* **90**, 71
Grave W, Nadorp J H S M & Rutten J J M H (1977) *Lancet* ii, 719
Grimson T A (1977) *Lancet* i, 858
Jones R H, Rudge C J, Bewick M, Parson V & Weston M J (1978) *British Medical Journal* i, 398–400
Kane P O (1961) *Journal of the Polarographic Society* **8**, 58
Leslie G B & Walker T F (1977) Proceedings of the Second International Symposium on Histamine H_2-Receptor Antagonists. Ed. W L Burland & M A Simkins. Excerpta Medica, Amsterdam; p 24
McMillen M A, Ambis D & Siegal J H (1978) *New England Journal of Medicine* **298**, 284
Randolph W C, Osborne V L, Walkenstein S S & Intoccia A P (1977) *Journal of Pharmaceutical Sciences* **66**, 1148
Smithers J L, Nichols P J & Maddocks J L (1975) *Journal of Pharmacy and Pharmacology* **27**, Suppl; p 36
Wood C A, Isaacson M L & Hibbs M S (1978) *Journal of the American Medical Association* **239**, 2550

CASE REPORT
dystonia, causes;
cimetidine, complications, dystonia

Exhibit J

Tagamet®-Induced Acute Dystonia

Stephen Romisher, MD*
Robert Felter, MD, FAAP†
James Dougherty, MD, FACEP*
Akron, Ohio

From the Department of Emergency Medicine, Akron General Hospital,* and the Division of Emergency/Trauma Services, Children's Hospital Medical Center of Akron,† Akron, Ohio.

Received for publication February 12, 1987. Accepted for publication June 2, 1987.

Address for reprints: Stephen Romisher, MD, Department of Emergency Medicine, Akron General Medical Center, 400 Wabash Avenue, Akron, Ohio 44307.

A 20-year-old woman presented with an apparent acute dystonic reaction after only five doses of cimetidine (Tagamet®). The patient was on no other medications with the exception of oral contraceptives. Emergency administration of IV diphenhydramine HCL brought rapid reversal of this acute dystonic reaction without any neurological sequelae. To our knowledge, this is the first reported case of an acute dystonic reaction associated with cimetidine. [Romisher S, Felter R, Dougherty J: Tagamet®-induced acute dystonia. Ann Emerg Med October 1987;16:1162-1164.]

INTRODUCTION

Since cimetidine was introduced, there have been numerous reports of neurologic side effects associated with its use.[1-7]

We report a case of cimetidine-associated acute dystonia in a patient after only 30 hours of therapy.

CASE REPORT

A 20-year-old woman was seen because of severe right-sided mandibular pain, ipsilateral trismus, and dysphonia.

The patient had been placed on ranitidine (Zantac®) 150 mg twice daily one week earlier because of suspected peptic ulcer disease. After four days of therapy, her physician discontinued the medication because she complained of intolerable gastrointestinal upset. Two days later, cimetidine (Tagamet®) 300 mg qid was started. The patient took the fifth dose 12 hours prior to admission. Approximately nine hours prior to admission, she noticed the sudden onset of right-sided mandibular pain. Several hours prior to admission, she developed right-sided trismus with associated dysphonia. When walking, there was involuntary turning in of her right foot.

300 mg 4x's/day
(1200 mg/day)

The medical history was significant only for a patent foramen ovale that was corrected surgically in childhood. Medications included oral contraceptives for more than one year and cimetidine. The patient denied the use of any other prescription or nonprescription medication or the use of illicit drugs. In addition, she denied mandibular trauma, fever, chills, or symptoms of orodental or pharyngeal pathology.

On physical examination, the patient's vital signs were as follows: pulse, 88; respirations, 18; blood pressure, 118/88 mm Hg; and temperature, 37.1 C. She was alert and oriented with impairment in phonation. There was marked spasm and pain of the right-sided masticatory muscles with deviation of the mandible to the right. The uvula was also deviated to the right, and there were tongue fasciculations. No lingual movements or dysphagia were noted. Pupils were equal and reactive and extraocular muscles were normal without any evidence of oculogyric dysfunction. The neck was supple without torticollis or retrocollis. Cardiac examination revealed a regular rhythm with a split first heart sound. Right ankle stiffening with "pipe-stem" rigidity was present despite normal reflexes with absent clonus in all four extremities. Gait testing revealed difficulty in ambulation because of a stiffened right ankle. The remainder of the physical examination was normal.

A urine screen for phenothiazines was obtained. A peripheral IV line of 5% dextrose and ½ normal saline was placed and she was given 50 mg of diphenhydramine HCl IV with immediate relaxation of the right-sided mus-

cles of mastication. There was marked improvement in phonation. The uvula remained deviated to the right, but there were no longer any tongue fasciculations. The right ankle showed absent rigidity to range of motion. No neurological abnormalities were found and gait testing was normal.

The patient was observed in the emergency department for approximately 90 minutes and discharged home with instructions to discontinue cimetidine and continue oral diphenhydramine HCl 50 mg four times per day for 48 hours. We re-examined the patient at 24 and 48 hours after her initial presentation. Complete return of normal speech and fifth cranial nerve function were noted. The uvula was in the mid-position and was no longer deviated.

Urine ferric chloride assay for phenothiazines done on admission was negative.

DISCUSSION

Acute dystonia is an extrapyramidal side effect (EPS) of antipsychotic medications and related compounds characterized by sudden, involuntary, intermittent tonus of a muscle or group of muscles.[8,10]

Any voluntary muscle group may be involved, but those of the head and neck are most frequently involved in adults.

Acute dystonias and dyskinesias are the least frequent but most dramatic forms of EPS.[8] However, dystonic reactions are now reported with increasing frequency when associated with neuroleptic use; rates may approach 50%.[11] Symptoms arise suddenly and may be frightening to the patient and observers.

Drugs that alter the dopamine-mediated function of the basal ganglia have been implicated in producing EPS. The drugs most notably responsible include neuroleptic agents used to treat psychosis, antiemetics such as trimethobenzamide and prochlorperazine, and the antireflux agent metaclopramide.[1,9,10,12] However, such other drugs as tricyclic antidepressants,[10] heroin,[13] benzodiazapines,[13] L-Dopa,[14] and ketamine[14] have been reported.[13]

The possibility of an acute dystonic reaction increases with increasing dosage and frequency but can occur after a single dose. Goldfrank and co-workers[15] believe the reactions are "idio-

reaction usually occurs within 24 to 72 hours of the first dose or after an increase in the maintenance dose.[9]

Cimetidine is a histamine receptor antagonist that is the structural analogue of histamine used in the treatment of peptic ulcer disease. The drug has no known effect on central dopaminergic pathways. CNS reactions have been reported with cimetidine therapy and are reversible on discontinuing the medication.[3] Predisposing factors to the development of this side effect include older age,[2,4] renal and hepatic impairment,[4,5] high-dose medication,[1,3] pre-existing psychiatric illness,[1,6] and simultaneous treatment with psychotropic medication.[1,6]

Only one previous case of extrapyramidal symptoms has been reported, and was associated with cerebellar syndrome.[7] These symptoms occurred in a 74-year-old man following a 1 g per day dose for 18 days. Renal and hepatic impairment were absent. However, the patient had preexisting cerebral vascular disease and dementia, and it was difficult to determine if cimetidine was the cause of the reaction. The patient had had previous acute confusional states.

Our patient was in excellent health with no predisposing factors in the development of acute dystonia or trismus. She had no history of neurologic or psychiatric illnesses. Infectious etiologies were not apparent. Toxicological screen was not obtained on other etiological agents that might cause an acute dystonic reaction because of the reliability of the patient's history. She was on no other medications that would confound the possibility of an acute dystonic reaction due solely to cimetidine. Finally, there was an adequate "wash out" period between the time she discontinued ranitidine and began cimetidine.

Emergency treatment of acute dystonia entails discontinuing the suspected offending agent and anticholinergic medication to offset cholinergic dominance. Parenteral diphenhydramine HCl or benztropine mesylate are the most familiar agents. However, other medications such as biperiden or trihexyphenidyl can be used.[9]

The emergency administration of diphenhydramine HCl 50 mg IM or slow IV push is one of the treatments of choice in adults.[9,12] Benztropine mesylate may be given as an alter-

Lee[14] to be the treatment of choice because of quicker recovery time and less drowsiness when compared to diphenhydramine HCL. Benztropine mesylate may be given at 2 mg IM or IV; however, the exact dose in children has not been fully documented.[9,10]

Despite the relatively rapid and dramatic recovery with these agents, there may be recurrences. To prevent them, Corre[10] recommends sending the patient home on oral diphenhydramine 50 mg three to four times daily for up to 72 hours.

eg. Schizophrenia

SUMMARY

We present a case of an acute extrapyramidal side effects associated with cimetidine. The presenting symptomatology was typical of EPS, and other potential causes of EPS such as drugs or underlying medical problems were not present. While certainly not occurring frequently in patients treated with cimetidine, it should be considered in the differential diagnosis of any patient presenting with an acute dystonic reaction.

The authors thank Pat Sage for preparation of the manuscript and Gordon Zellers, MD, for technical assistance on this case.

REFERENCES

1. AMA Drug Evaluations, ed 5. Chicago: American Medical Association, 1983, p 1265-1268.

ok 2. Sonnenblick M, Weissberg N, Rosin AJ. Neurological and psychiatric side effects of cimetidine report of three cases with review of the literature. Postgrad Med J 1982;58:415-418.

3. Jenike MA. Cimetidine in elderly patients. Review of uses and risks. J Am Geriatr Soc 1982;30:170-173.

4. Edmonds ME, Ashford RFU, Brenner MK, et al. Cimetidines: Does neurotoxicity occur? Report of three cases. J Royal Soc Med 1979;72:172-175.

5. Larsson R, Bodemar G, Kagedal B, et al. The effects of cimetidine (Tagamet) on renal function in patients with renal failure. Acta Med Scand 1980;208:27-31.

6. Titus JP. Cimetidine induced mania in depressed patients. J Clin Psychiatry 1985;44:267-268.

7. Handler CE, Besse CP, Wilson AO. Extrapyramidal and cerebellar syndrome with encephalopathy associated with cimetidine. Postgrad Med J 1982;58:527-528.

8. Gregory I, Smeltzer DJ (eds). Psychiatry: Essentials of Clinical Practice. Boston: Little, Brown and Co, 1977, p 107-110.

9. Mack RB. Acute dystonia: A statue with limitations. Contemporary Pediatrics 1985

10. Corre KA, Niemann JT, Bessen HA: Extended therapy for acute dystonic reactions. *Ann Emerg Med* 1984;13:104-107.

11. Sramek JJ, Simpson GM, Morrison RL, et al: Anticholinergic agents for prophylaxis of neuroleptic induced dystonic reactions: A prospective study. *J Clin Psychiatry* 1986;47:305-309.

12. Baldessarini RJ: Drugs and the treatment of psychiatric disorders, in Gilman AG, Goodman LS, Gilman A (eds): *The Pharmacological Basis of Therapeutics*, ed 6. New York, MacMillan Publishing Co, Inc, 1980, p 391-447.

13. Lee A: Treatment of drug induced dystonic reactions. *JACEP* 1979;8:453-457.

14. Felser JM, Orban DJ: Dystonic reaction after ketamine abuse. *Ann Emerg Med* 1982;11:673-675.

15. Goldfrank L, Flomenbaum N, Weisman R: Management of overdose with psychoactive medications. *Emerg Med Clin North Am* 1984;2:63-76.

American Board of Emergency Medicine Notice

On June 30, 1988, the practice option will terminate for those physicians wishing to meet the credential requirements of the

The Journal of Emergency Medicine, Vol. 21, No. 1, pp. 27–29, 2001

0736-4679/01 $–see front matter

PII S0736-4679(01)00325-0

Edubf K

Selected Topics: Toxicology

CIME "antidotes"

Given I.V., Cime induces AE's at lower dosages (see Porter et al., 1986)

CIMETIDINE-INDUCED DYSTONIC REACTION

Ralph S. Peiris, DO* and Bradley F. Peckler, MD†

*Department of Emergency Medicine, St. Barnabus Hospital and †Department of Emergency Medicine, Lincoln Hospital and Mental Health Center, Bronx, New York

Reprint Address: Bradley F. Peckler, MD, Department of Emergency Medicine, Lincoln Hospital and Mental Health Center, 234 E. 149th Street, Bronx, NY 10451

Abstract—A 39-year-old woman presented to the Emergency Department complaining of nausea and vomiting. The patient was given intravenous cimetidine for epigastric pain and subsequently developed a dystonic reaction. Administration of cimetidine, an H2 receptor antagonist, is an uncommon cause of dystonic reaction. We discuss the pathophysiology, diagnosis, and treatment. © 2001 Elsevier Science Inc.

Keywords—cimetidine; dystonic reaction; H-2 blockers

INTRODUCTION

Dystonic reactions are typically described as sustained abnormal postures and disruptions of movement resulting from alterations in muscle tone. The most common manifestations of dystonia are bizarre muscle spasms of the head, neck, and tongue, causing oculogyric crises, torticollis, swallowing or chewing difficulties, and masseter spasms, respectively. Younger patients are at higher risk than are older ones (1). Acute dystonia is a dramatic form of extrapyramidal side effects of antipsychotic medications (1). High potency antipsychotics (haloperidol and fluphenazine) and antiemetics (prochlorperazine and metoclopramide) are traditionally the most common drugs implicated in dystonic reactions (1,2). Cimetidine is not a common cause of dystonic reaction; however, there are a handful of reports implicating type 2 histamine antagonists as a cause of dystonia and other extrapyramidal syndromes, but there is no agreement on the pathophysiology of this reaction (3–8). We present a case of dystonic reaction induced by cimetidine given intravenously (i.v.) and a brief discussion of dystonic reactions, proposed pathophysiologic mechanisms, and treatment of this disorder.

CASE PRESENTATION

A 39-year-old woman presented via ambulance to the Emergency Department (ED) with a chief complaint of nausea and vomiting with epigastric pain for the last 3 days. The patient had not taken her antiepileptic medication for 5 days and had a seizure 1 h prior to arrival. The patient had presented to the ED 1 week prior for the same complaints.

During her previous visit to the ED, the patient was given i.v. prochlorperazine for the multiple episodes of nausea and emesis. She had a dystonic reaction described as "lip smacking," or masseter spasms, and an oculogyric crisis within 5–7 min of administration of prochlorperazine. The patient was given 50 mg diphenhydramine intramuscularly, and the symptoms resolved completely within 5 min. She was admitted to the hospital for intractable vomiting, restarted on her seizure medications, and subsequently discharged.

Since the dystonic reaction of the prior week, the patient denied any similar reactions, psychiatric history,

Selected Topics: Toxicology is coordinated by *Kenneth Kulig*, MD, of Denver Colorado

Received: 25 August 2000; Final submission received: 29 December 2000;
Accepted: 31 January 2001

or any use of antipsychotic medication. She did not use antiemetics before coming to the ED. The patient also denied any illicit drug or alcohol use, but admitted to smoking one pack of cigarettes per day. Her medications included an albuterol inhaler for asthma, alprazolam for ED anxiety, and phenytoin for epilepsy.

Physical examination revealed a well-developed woman in no acute distress. Vital signs were blood pressure of 140/91 mm Hg, pulse of 94 beats/min, respiratory rate of 18 breaths/min, and an oral temperature of 36.5°C (97.7°F). The physical examination was unremarkable except for mild epigastric tenderness with no guarding or rebound tenderness. The rectal examination was hemoccult negative with brown stool and good sphincter tone.

An i.v. line was placed and blood work (CBC with differential, SMA 7, phenytoin level, amylase, and lipase) was sent to the laboratory. Intravenous normal saline and i.v. cimetidine 300 mg were ordered.

Within 5 min of administrating cimetidine 300 mg i.v., the patient experienced a dystonic reaction similar to the reaction she had when prochlorperazine was administered. The patient initially had masseter spasm with mild lip smacking and then experienced an oculogyric crisis. She also experienced a mild neck spasm during the dystonic reaction.

The i.v. cimetidine was immediately stopped, and the patient was administered diphenhydramine 50 mg i.v. along with 2 mg of lorazepam i.v., which relieved her dystonic reaction within 5 min of administration. Steps were taken to ascertain whether an error was made in administration of another medication. There was a written order for cimetidine. Medication in our ED is dispensed through the Pyxis system, which takes into account a patient's allergies and delivers medication from computerized and labeled slots. All activity is recorded and can be reviewed. This is to prevent incorrect or possibly harmful medication being given to a patient. After extensive review by the nurse, resident physician, and the attending physician, we concluded that the patient did indeed receive cimetidine.

The laboratory data revealed no significant changes compared to the results of 1 week ago. After the resolution of the dystonic reaction, she remained asymptomatic during the hospital stay. The patient was loaded with phenytoin, and was discharged 8 hours later after tolerating oral fluids. She was given diphenhydramine to continue after discharge.

DISCUSSION

Dystonic reactions are adverse extrapyramidal side effects that can occur shortly after the initiation of neuroleptic drug therapy and may occur with a wide variety of medications. Acute dystonic reactions are characterized by intermittent spasmodic or sustained involuntary contractions of muscles in the face, neck, trunk, pelvis, and extremities. In adults, the head and neck muscles are the most frequently involved (1). Although dystonic reactions are rarely life threatening, they are very uncomfortable and often produce significant anxiety and distress for patients.

Drugs that alter the dopaminergic-cholingeric balance in the nigro-striatal pathway (in the basal ganglia) have been implicated in producing extrapyramidal side effects. Most drugs produce dystonic reactions by nigrostriatal D2-dopamine receptor blockade, which leads to an excess of striatal cholinergic output. It remains unclear if dystonia is caused by the relative relationship of the two receptors or by an excess or lack of one of the components (9). The drugs often implicated in causing dystonic reactions are high potency D2-receptor antagonists, including neuroleptic agents; antiemetics, such as prochlorperazine and trimethobenzamide; and the antireflux agent, metoclopramide (2,9,10). Any agent that balances dopamine blockade with M1-muscarinic receptor blockade is less likely to produce a dystonic reaction.

van't Groenewout et al., using selective microinjection to different areas of the basal ganglia, demonstrated in a rat model that the antihistamine properties of both diphenhydramine (H1) and cimetidine (H2) can have antidystonic effects (11). In the same paper they reproted that the anticholinergic medicine had no effect on dystonia. Davis et al. reported a case of a cranial dystonia caused by ranitidine and suggested that the location of the anticholinergic or dopaminergic effects of the drug may play a role in causing dystonia (6).

Dystonic reactions are more likely to occur with increasing dosage and frequency, but may occur after a single dose. Goldfrank et al. believed that dystonic reactions are often "idiosyncratic" (12). These reactions usually occur within 24–72 h and may even occur as late as 5 days after the first dose or after an increase in the maintenance dose.

Cimetidine is a histamine type-2 receptor antagonist used in the treatment of gastric and duodenal ulcers and is considered the drug of choice for the treatment of an uncomplicated peptic ulcer (13). The drug produces no known alterations of the central dopaminergic pathways (11). Central nervous system reactions, such as coarse postural and action tremors, and involuntary motor symptoms, including dystonia, have been reported with cimetidine therapy (7,8,10). Side effects are typically reversible on discontinuation of the medication. Predisposing factors for such reactions include older age, renal and hepatic impairment, higher dosages, pre-existing psychiatric illness, and simultaneous treatment with psy-

chotropic medication (10). Our patient had none of these characteristics, and the alprazolam that she was taking might be considered as protective against a dystonic reaction.

In our case the dystonic reaction was very likely caused by the cimetidine. It was the only medication that was given because the patient was unable to tolerate anything by mouth. It is unlikely that the patient's previous dystonic reaction to prochlorperazine 1 week earlier was related because of the asymptomatic period between the episodes and because of the temporal relationship to cimetidine.

Treatment of dystonic reactions involves discontinuing the suspected offending drug and giving an anticholinergic agent to suppress the increased cholinergic output. Securing the airway may be necessary with laryngeal and pharyngeal dystonic reactions when respiratory compromise occurs. Usually pharmacological treatment, such as diphenhydramine HCl or benztropine mesylate, is needed to resolve the reaction. Other medications used in the treatment of dystonic reaction include trihexylphenidyl; biperiden; or benzodiazepines, such as diazepam or lorazepam (12).

Despite dystonic reactions resolving rapidly after a single dose of anticholinergic medicine, the suspected medicine must be discontinued, and anticholinergics must be continued for 48–72 h to prevent a relapse (14).

SUMMARY

We present a case of a dystonic reaction associated with cimetidine administration. The mechanism of dystonic reactions is most commonly attributed to a disruption of the dopaminergic-cholinergic neuropathways in the basal ganglia. The exact neurochemical problem and location in the brain have yet to be identified. Though not common, cimetidine must be considered as a potential cause of dystonia. Because cimetidine has been approved for over-the-counter use, it is possible that more dystonic reactions caused by this drug will occur.

REFERENCES

1. Noctimson G, Keim S. Dystonic reactions. emedicine.com 2000.
2. Lucke W, Hockberger R. Thought disorders. Rosen's emergency medicine concepts and clinical practice. 4th edn., 1992,2817–23.
3. Romisher S, Fetter R, Dougherty J. Tagamet induced acute dystonia. Ann Emerg Med 1987;16:1162–3.
4. Kapur V, Barber K, Peddireddy R. Ranitidine-induced acute dystonia. Am J Emerg Med 1999;17:258–60.
5. Wilson LB, Woodward AM, Ferrara JJ. An acute dystonic reaction with long-term use of ranitidine in an intensive care unit patient. J La State Med Soc 1997;149:36–8.
6. Davis BJ, Aul EA, Granner MA, Rodnitzky RL. Ranitidine-induced cranial dystonia. Clin Neuropharmacol 1994;17:489–91.
7. Batemna DN, Bevan P, Longley BP, Mastaglia, Wandless I. Cimetidine induced postural and action tremor. J Neurol Neurosurg Psychiatry 1981;44:94.
8. Kushner MJ. Chorea and cimetidine. Ann Intern Med 1982;96:126.
9. Diederich NJ, Goetz CG. Drug-induced movement disorders. Neuro Clinics 1998;16:125–39.
10. Sonnenblick M, Rosin AJ, Weissberg N. Neurological and psychiatric side effects of cimetidine-report of 3 cases with review of the literature. Postgrad Med J 1982;58:415–18.
11. van't Groenwout JL, Stone MR, Vo VN, Truong DD, Matsumoto RR. Evidence for the involvement of histamine in the antidystonic effects of diphenhydramine. Exp Neurol 1995;134:253–60.
12. Goldfrank L, Flomenbaum N, Weisman R. Management of overdose with psychoactive medications. Emerg Med Clin North Am 1984;2:63–76.
13. American Medical Association. AMA drug evaluations. 6th edn. Chicago: American Medical Association; 1986:935–7.
14. Cotre KA, Niemann JT, Bessen HA. Extended therapy for acute dystonic reactions. Ann Emerg Med 1984;13:194–7.

Cime induced dystonia
Antidotes, named in
[illegible]
that can be [illegible]
with [illegible] movement
disorders

Exh L

Database	Ovid MEDLINE(R) 1966 to Present with Daily Update
Unique Identifier	1457266
Authors	Pacifici GM. Donatelli P. Giuliani L.
Institution	Department of Biomedicine, Medical School, University of Pisa, Italy.
Title	Histamine N-methyl transferase: inhibition by drugs.
Source	British Journal of Clinical Pharmacology. 34(4):322-7, 1992 Oct.
Abbreviated Source	Br J Clin Pharmacol. 34(4):322-7, 1992 Oct.
MeSH Subject Headings	Adult Aged Female *Histamine N-Methyltransferase / an [Analysis] *Histamine N-Methyltransferase / ai [Antagonists & Inhibitors] Humans Male Middle Aged Research Support, Non-U.S. Gov't Tissue Distribution
Abstract	1. Histamine N-methyl transferase activity was measured in samples of human liver, brain, kidney, lung and intestinal mucosa. The mean (+/- s.d.) rate (nmol min-1 mg-1 protein) of histamine N-methylation was 1.78 +/- 0.59 (liver, n = 60), 1.15 +/- 0.38 (renal cortex, n = 8), 0.79 +/- 0.14 (renal medulla, n = 8), 0.35 +/- 0.08 (lung, n = 20), 0.47 +/- 0.18 (human intestine, n = 30) and 0.29 +/- 0.14 (brain, n = 13). 2. Inhibition of histamine N-methyl transferase by 15 drugs was investigated in human liver. The IC50 for the various drugs ranged over three orders of magnitude; chloroquine was the most potent inhibitor. 3. The average IC50 values for chloroquine were 12.6, 22.0, 19.0, 21.6 microM in liver, renal cortex, brain and colon, respectively. These values are lower than the Michaelis-Menten constant for histamine N-methyltransferase in liver (43.8 microM) and kidney (45.5 microM). Chloroquine carried a mixed non-competitive inhibition of hepatic histamine N-methyl transferase. Some side-effects of chloroquine may be explained by inhibition of histamine N-methyl transferase.
Publication Type	Journal Article.
Entry Date	19930112

Exh M

Am J Physiol Lung Cell Mol Physiol 267: L342-L349, 1994;
1040-0605/94 $5.00

AJP - Lung Cellular and Molecular Physiology, Vol 267, Issue 3 342-L349,

ARTICLES

Structure and function of human histamine N-methyltransferase: critical enzyme in histamine metabolism in airway

K. Yamauchi, K. Sekizawa, H. Suzuki, H. Nakazawa, Y. Ohkawara, D. Katayose, H. Ohtsu, G. Tamura, S. Shibahara, M. Takemura and al. et
First Department of Internal Medicine, Tohoku University School of Medicine, Sendai, Japan.

In mammals, histamine is inactivated principally by two enzymes: histamine N-methyltransferase (HMT; EC 2.1.1.8) and diamine oxidase (DAO; EC 1.4.3.6.). The cDNA clone of human HMT (hHMT) has been isolated from a cDNA library of human kidney and its nucleotide, and deduced amino acid sequences have been determined. One clone, phHMT-1, containing an insert of 1.4 kb, was confirmed to encode HMT by transient expression of HMT activity in COS cells. hHMT consists of 292 amino acid residues [relative molecular weight (M(r)) = 33,279] and shares 82% identity with that of rat HMT. Northern blot analysis with hHMT cDNA probe revealed that 1.6-kb HMT mRNA transcript was expressed in the lung, nasal polyps, and kidney. HMT activity was measured in human trachea and bronchi. In addition, the contractile response of isolated human bronchi to histamine was potentiated in the presence of an HMT inhibitor, SKF 91488, but a DAO inhibitor, aminoguanidine, was without effect. These results suggest that HMT plays an important role in degrading histamine and in regulating the airway response to histamine. Therefore, the level of HMT gene expression in human airway may be one of the critical factors determining the airway responsiveness to histamine. In situ chromosomal hybridization demonstrated that human HMT gene was localized in chromosome 1 p32.

This article has been cited by other articles: (Search Google Scholar for Other Citing Articles)

GUT An International Journal of Gastroenterology and Hepatology ▸HOME

S Komatsu, M B Grisham, J M Russell, and D N Granger
Enhanced mucosal permeability and nitric oxide synthase activity in jejunum of mast cell deficient mice
Gut, November 1, 1997; 41(5): 636 - 641.
[Abstract] [Full Text] [PDF]

MOLECULAR PHARMACOLOGY ▸HOME

C. V. Preuss, T. C. Wood, C. L. Szumlanski, R. B. Raftogianis, D. M. Otterness, B. Girard, M. C. Scott, and R. M. Weinshilboum
Human Histamine N-Methyltransferase Pharmacogenetics: Common Genetic Polymorphisms that Alter Activity
Mol. Pharmacol., April 1, 1998; 53(4): 708 - 717.
[Abstract] [Full Text]

EXHIBIT N

The page you requested will not function properly unless you enable JavaScript in your browser. Please visit the Site map to navigate this site.

Go

Search

MY LINKS | E-CARDS | POLLS | QUIZ | HELP | COMME

Glossary of dementia terms

- Abstracting
- Acetyl coenzyme A
- Acetylcholine (ACh)
- Acetylcholinesterase (AChE)
- Acetylcholinesterase inhibitors (AChEIs)
- Acquired immune deficiency syndrome (AIDS)
- Action potential
- ADAS-cog
- Agitation
- Agnosia
- Agonist
- Allele
- Allosteric
- Alzheimer's disease (AD)
- Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS/ADL) inventory
- Amygdala
- Amyloid precursor protein (APP)
- Antagonist
- Anti-amyloid agents
- Anticholinergic drugs
- Anticholinergic side effect
- Anticonvulsant
- Antidepressant
- Antipsychotics
- Apathy
- Aphasia
- Apolipoprotein
- Apolipoprotein E gene (ApoE)
- Apraxia
- Aricept
- Astrocyte
- ATP
- Autopsy
- Axon
- Axon terminal
- Baptist theory
- Basic activities of daily living (ADL)
- Behavioral symptoms
- Benzodiazepines
- Beta-amyloid peptide (beta-A4 and A-beta)
- Beta-amyloid plaques
- Binswanger (type subcortical dementia)
- Bioavailability
- Brain stem
- Butyrylcholinesterase (BChE)
- Caregiver burden
- Catatonic
- Central nervous system (CNS)
- Cerebellum
- Cerebral
- Cerebral cortex
- Cerebrospinal fluid (CSF)
- Cerebrovascular disease
- Cerebrum
- Choline acetyltransferase (ChAT)
- Cholinergic
- Cholinomimetic
- Chromosome
- CIBIC-plus
- Cimetidine
- Cognex
- Cognition
- Cognitive tests
- Competitive inhibition
- Computed tomography (CT)
- Computerized axial tomography (CAT)

- Constructional difficulties
- Cortical
- Cortical atrophy
- Cost effectiveness
- Creutzfeldt-Jakob disease (CJD)
- Cytochrome P450
- Delirium
- Delusions
- Dementia
- Dendrites
- Depolarization
- Depression
- Digoxin
- Direct costs
- Disability Assessment for Dementia (DAD)
- Disinhibition
- Donepezil
- Dopamine
- Double-blind
- Down's syndrome
- Drift
- Dysarthria
- Dysexecutive syndrome
- Dysphagia
- Dysphasia
- Dysphoria
- Dyspraxia
- Enrichment trial design
- Estrogen
- Euphoria
- Executive function
- Exelon
- Extrapyramidal syndrome
- FADH2
- Field cut
- Folate
- Food and Drug Administration (FDA)
- Frontal lobe dementia
- Frontal lobes
- Functional Assessment Scale (FAST) scale
- Functional neuroimaging
- GAL-9505
- GAL-INT-1
- GAL-INT-2
- GAL-USA-1
- GAL-USA-1/3
- GAL-USA-10
- Galantamine
- Gamma-aminobutyric acid (GABA)
- Genes
- Genetic mutation
- Genotype
- Geriatrician
- Gingko biloba
- Glial cells
- Global functioning
- Glutamate
- Glutamine
- Gyri
- Half-life
- Hallucinations
- Hematological
- Hemiplegia
- Hemiplegic
- Hepatic
- Hepatic encephalopathy
- Hepatotoxic
- Heterozygous
- Hippocampus
- Histological marker
- Homozygous
- Human Immunodeficiency Virus (HIV)
- Huntington's disease
- Hydrocephalus
- Hydrolysis
- Hyperactivity
- Hypoactivity
- Hypokinesia
- Hypothalamus
- Hypothyroidism
- Idiopathic
- Incontinence
- Indirect costs
- Inflammatory mediators
- Insomnia
- Institutionalization
- Instrumental activities of daily living (IADL)
- Intention-to-treat analysis (ITT)
- Intrathecal
- Ischemia
- Ketoconazole
- Lacunar infarct
- Lacunar state dementia
- Last-observation carried forward (LOCF)

Lewy bodies	Lewy body disease
Limbic system	Macroglia
Magnetic resonance imaging (MRI) scan	Medicaid
Menopause	Metabolism
Metabolite	Metrifonate
Microglia	Microtubules
Mini-Mental State Examinations (MMSE)	Mixed dementia
Monoamine oxidase B (MAO-B)	Monoamine oxidase inhibitors (MAOIs)
Muscarinic receptors	Muscular dystrophy
Myasthenia gravis	N-methyl-D-aspartate (NMDA)
N6D compounds	N7D compounds
NADH	Nerve growth factor (NGF)
Neurodegenerative disease	Neurofibrillary tangles (NFTs)
Neuroimaging	Neurological
Neurologist	Neuron
Neuropsychiatric inventory (NPI)	Neuropsychiatric Inventory Caregiver Distress Scale (NPI-D)
Neuropsychiatric symptoms	Neuropsychiatrist
Neuropsychologist	Neuropsychometric tests
Neurotransmitters	Neurotrophic agents
Nicotinic receptor	NINCDS-ADRDA criteria
Non-steroidal anti-inflammatory drugs (NSAIDs)	Nootropics
Noradrenaline (norepinephrine)	Oligodendrocytes
Oxidative damage	Oxidative phosphorylation
Paired helical filaments	Parallel study
Paranoia	Parietal
Parkinson's disease	Paroxetine
Pathogenesis	Pathology
Peripheral nervous system (PNS)	Perseveration
Pharmacokinetics	Pharmacology
Pharmacotherapy	Phenotype
Phobia	Phospholipid
Physostigmine	Pick's disease
Pittsburgh Sleep Quality Index (PSQI)	Placebo controlled
Polio (poliomyelitis)	Positron emission tomography (PET)
Postsynaptic membrane	Presenelin-1 (PS1) gene
Presenelin-2 (PS2) gene	Presynaptic membrane
Progressive deterioration scale (PDS)	Psychiatrist
Psychosis	Psychosocial
Pyruvate	Radical scavengers
Randomized-start trial	Randomized-withdrawal trial
Reality therapy	Receptors
Reflex assymetry	Reminiscence therapy
Reminyl	Renal
Reversible inhibitor	Rivastigmine
Robust analysis	Sabeluzole
Secretase	Selective serotonin re-uptake inhibitors (SSRIs)

Serotonin (5-hydroxytryptamine, 5-HT)
Single photon emission computed tomography (SPECT)
Striated muscle
Stroke
Structural imaging
Subdural hemorrhage
Substance P
Sulcus
Supranuclear
Synapse
Synaptic cleft
Synaptic vesicles
Syphilis
Tacrine
Tau
Temporal lobes
Thalamus
Thyroid
Tricyclic antidepressants
Trigeminal neuralgia
Trisomy
Ubiquitin
Validation therapy
Vascular dementia
Ventricles
Visuospatial difficulties
Vitamin B12
Warfarin

Abstracting

The power of abstract thinking, including understanding of known idiom and non-literal expressions. For example, this would include understanding an expression such as "Rome wasn't built in a day" for its intended meaning rather than its literal meaning.

Acetyl coenzyme A

Acetyl coenzyme A (acetyl CoA) is an important metabolic intermediate that performs a variety of biological functions including feeding into the tricarboxylic acid cycle to generate ATP.

Acetylcholine (ACh)

A neurotransmitter vital for correct brain functioning, which is involved in learning and memory. Levels of ACh are progressively depleted in the brains of patients with AD. The actions of ACh are termed cholinergic and can be blocked by anticholinergic drugs.

Acetylcholinesterase (AChE)

The enzyme responsible for hydrolyzing and inactivating acetylcholine in the synaptic cleft.

Acetylcholinesterase inhibitors (AChEIs)

A class of drugs that block the action of the acetylcholinesterase enzyme in the synaptic cleft, therefore increasing the level of acetylcholine in the brain.

Acquired immune deficiency syndrome (AIDS)

A deficiency of the immune system that occurs as a result of infection with human immunodeficiency virus (HIV).

Action potential

A localized change in electrical potential transmitted along the axon of the neuron triggered by stimulation (touch, pain, cold, etc.). Action potentials facilitate communication between cells by stimulating the release of neurotransmitters into the synaptic cleft. An action potential is caused

by a change in the permeability of the membrane to sodium and potassium ions.

ADAS-cog

The cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) is used in clinical trials to measure the cognitive and neuropsychological benefits of treatment. The ADAS-cog scale consists of a battery of individual tests, including tests of recall, naming, commands, orientation, word recognition, spoken language and comprehension, word finding and recall of test instructions.

Agitation

Motor or vocal behavior (screaming, complaining, cursing, fidgeting, shouting, moaning, pacing, wandering) that is either disruptive, unsafe or interferes with the delivery of care in a particular environment. Agitation is a non-specific symptom of one or more physical or psychological processes.

Agnosia

Failure of recognition, especially of people.

Agonist

A drug that binds to a receptor and activates it, producing a biochemical response.

Allele

Any one of a series of two or more different genes that occupy the same position (locus) on a chromosome.

Allosteric

Allosteric means 'spatially distinct'. Thus, an allosteric binding site is a site on a receptor that is different from the substrate binding site, e.g. Reminyl binds at a site on the pre-synaptic nicotinic receptor that is different from the acetylcholine binding site.

Alzheimer's disease (AD)

AD is a progressive neurodegenerative condition characterized clinically by a gradual decline in cognition, daily functioning and behavior. AD is the most common cause of dementia.

Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS/ADL) inventory

A scale used in clinical trials to assess the efficacy of a drug treatment on daily functioning. Used to assess a number of areas of daily functioning, including both instrumental and basic ADL, and has been tested and validated in patients with mild-to-moderately severe AD. Using the ADCS/ADL, the clinician assesses the patient by interviewing the patient's primary caregiver. Used in GAL-USA-10 to assess the efficacy of Reminyl on daily functioning over 5 months.

Amygdala

A lobe of the cerebrum. In AD, amyloid deposits develop in the extracellular spaces of the amygdala and NFTs develop within neurons.

Exhibit O

http://0-www.thomsonhc.com.library.uchsc.edu/hcs/librarian/ND_PR/Interactions/PFPUI/GS3yvvh15RFBMb/ND_PG/PRIH/CS/915B2D/ND_CPR/S

To content

[x] Thomson MICROMEDEX Logo

MICROMEDEX® Healthcare Series

» My Thomson Gateway
VisualDx®
× Log Out

[x] Main.	[x] Drugs.	[x] Toxicology.	[x] Disease.	[x] Lab.	[x] IV Compatibility.	[x] Interactions.	[x] Patient Education.	[x] Formulary & Handheld.
	[x] Drugs.	[x] Toxicology.	[x] Disease.	[x] Lab.		[x] Interactions.	[x] Patient Education.	[x] Formulary & Handheld.

[x] Print Ready Document. Print ReadyPrint Ready [x] Help. Page Help

Search Path : Check Interactions (Single) >
Single Interactions Table

[x] Modify Your Search.

Checking Interactions For:

- Chloroquine Phosphate
[CHLOROQUINE PHOSPHATE]

All Severities (contraindicated through minor)
All Documentation (excellent through unlikely)

Go To Interaction Type:

Click on a link to skip to Interaction.
Drug-Drug Interactions *(50 results)*
(9 contraindications)
Drug-Pregnancy Interactions *(1 result)*
Drug-Lactation Interactions *(1 result)*

Drug-Drug Interactions: (50 results) (9 contraindications)

back to top

Interaction	Severity	Documentation	Summary
Chloroquine Phosphate			
	CONTRAINDICATED	FAIR	*Concurrent use of AUROTHIOGLUCOSE and CHLOROQUINE may result in an increased risk of blood dyscrasias.*
Chloroquine Phosphate			

	CONTRAINDICATED	FAIR	*Concurrent use of LEVOMETHADYL and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**CONTRAINDICATED**	FAIR	*Concurrent use of BEPRIDIL and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**CONTRAINDICATED**	FAIR	*Concurrent use of CHLOROQUINE and CISAPRIDE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**CONTRAINDICATED**	FAIR	*Concurrent use of CHLOROQUINE and THIORIDAZINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**CONTRAINDICATED**	FAIR	*Concurrent use of CHLOROQUINE and MESORIDAZINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**CONTRAINDICATED**	FAIR	*Concurrent use of CHLOROQUINE and PIMOZIDE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**CONTRAINDICATED**	FAIR	*Concurrent use of TERFENADINE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**CONTRAINDICATED**	FAIR	*Concurrent use of ZIPRASIDONE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	GOOD	*Concurrent use of CHLOROQUINE and CIMETIDINE may result in*

			chloroquine toxicity (agitation, seizures, cardiac arrest).
Chloroquine Phosphate	**MAJOR**	GOOD	*Concurrent use of HALOFANTRINE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	GOOD	*Concurrent use of GEMIFLOXACIN and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	GOOD	*Concurrent use of ISOFLURANE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of CHLORAL HYDRATE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of LIDOFLAZINE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of DROPERIDOL and ANTIMALARIALS may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of ASTEMIZOLE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of RABIES VACCINE and CHLOROQUINE may result in decreased antibody response.*

Chloroquine Phosphate

	MAJOR	FAIR	*Concurrent use of MEFLOQUINE and CHLOROQUINE may result in an increased risk of convulsions, electrocardiogram abnormalities, cardiac arrest.*
Chloroquine Phosphate			
	MAJOR	FAIR	*Concurrent use of ERYTHROMYCIN and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate			
	MAJOR	FAIR	*Concurrent use of PENTAMIDINE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate			
	MAJOR	FAIR	*Concurrent use of OCTREOTIDE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate			
	MAJOR	FAIR	*Concurrent use of FOSCARNET and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate			
	MAJOR	FAIR	*Concurrent use of CHLOROQUINE and PROBUCOL may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate			
	MAJOR	FAIR	*Concurrent use of CHLOROQUINE and CLASS III ANTIARRHYTHMIC AGENTS may result in cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate			
	MAJOR	FAIR	*Concurrent use of CHLOROQUINE and TRICYCLIC ANTIDEPRESSANTS may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate			

	MAJOR	FAIR	*Concurrent use of CHLOROQUINE and VASOPRESSIN may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of CHLOROQUINE and VENLAFAXINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of CHLOROQUINE and FLUCONAZOLE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of COTRIMOXAZOLE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of CHLOROQUINE and CLASS IA ANTIARRHYTHMIC AGENTS may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of CHLOROQUINE and CLARITHROMYCIN may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of ARSENIC TRIOXIDE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of CHLOROQUINE and ANTIPSYCHOTICS may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of ISRADIPINE and CHLOROQUINE may result in an*

			increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of CHLOROQUINE and PHENOTHIAZINES may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of CHLOROQUINE and CLASS I ANTIARRHYTHMIC AGENTS may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of CHLOROQUINE and FLUOXETINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of SPIRAMYCIN and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of CHLOROQUINE and DOLASETRON may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of HALOTHANE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of ZOLMITRIPTAN and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of TELITHROMYCIN and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de*

Interaction	Severity	Documentation	Summary
			pointes, cardiac arrest).
Chloroquine Phosphate	**MAJOR**	FAIR	*Concurrent use of ENFLURANE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).*
Chloroquine Phosphate	MODERATE	GOOD	*Concurrent use of CHLOROQUINE and CYCLOSPORINE may result in an increased risk of cyclosporine toxicity (renal dysfunction, cholestasis, paresthesias).*
Chloroquine Phosphate	MODERATE	GOOD	*Concurrent use of CHLOROQUINE and KAOLIN may result in decreased efficacy of chloroquine.*
Chloroquine Phosphate	MODERATE	GOOD	*Concurrent use of CHLOROQUINE and PROGUANIL may result in increased incidence of mouth ulcers.*
Chloroquine Phosphate	MODERATE	GOOD	*Concurrent use of CHLOROQUINE and PRAZIQUANTEL may result in decreased praziquantel bioavailability.*
Chloroquine Phosphate	MODERATE	GOOD	*Concurrent use of CHLOROQUINE and ANTACIDS may result in decreased efficacy of chloroquine.*
Chloroquine Phosphate	MINOR	GOOD	*Concurrent use of LEVOTHYROXINE and CHLOROQUINE may result in an increase in the thyroxine stimulating hormone level and decreased levothyroxine effectiveness.*

Drug-Pregnancy Interactions: (1 result)

back to top

Interaction	Severity	Summary
Chloroquine Phosphate	MODERATE	*Chloroquine is rated as US FDA Category C. Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. (OR) No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.*

Drug-Lactation Interactions: (1 result)

Interaction	Severity	Summary
Chloroquine Phosphate		
	MAJOR	*According to the American Academy of Pediatrics, Chloroquine is compatible with breast-feeding.*

back to top

Home | Contact Us | Content Updates | Training Center | Warranty and Disclaimer | Editorial Info | About Us | Help | Log Out